

## **Evidence Report:**

### ***Risk of Reduced Physical Performance Capabilities Due To Reduced Aerobic Capacity***

#### **Human Research Program Human Health Countermeasures Element**

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## **I. PRD Risk Title: Risk of Reduced Physical Performance Capabilities Due to Reduced Aerobic Capacity**

Astronauts' physical performance during a mission, including activity in microgravity and fractional gravity, is critical to mission success. A decrease in maximal aerobic capacity ( $\text{VO}_2\text{peak}$ ) affects the astronauts' ability to perform prolonged tasks as well as shorter bouts of higher intensity activity that may be required during extravehicular activities (EVAs) on the International Space Station (ISS) and during future exploration missions and emergency egress scenarios. Accurate assessments of  $\text{VO}_2\text{peak}$  during the mission are needed to evaluate astronauts' readiness to perform mission-critical tasks relative to pre-flight.

## **II. EXECUTIVE SUMMARY**

Maintenance of maximal aerobic capacity ( $\text{VO}_2\text{peak}$ ) during and after spaceflight is a significant concern to NASA for both the ISS era and during future exploration missions. Even relatively small decreases in  $\text{VO}_2\text{peak}$  (i.e., 10%) may impact tolerance to extended work and the ability to meet high-energy demands during mission-critical tasks. Data from the Shuttle era indicated that  $\text{VO}_2\text{peak}$  was maintained during short-duration spaceflight but was impaired after landing, perhaps due to the combined effects of orthostatic stress and relative hypovolemia. According to the current medical requirement, changes in astronauts' aerobic fitness are estimated during ISS missions based on the heart rate (HR) response to submaximal exercise. ISS astronauts typically demonstrate an elevated HR response to submaximal exercise, suggesting a reduction in  $\text{VO}_2\text{peak}$ . Importantly, this estimation method is not an accurate predictor of  $\text{VO}_2\text{peak}$ . In fact, this method was shown to produce errors in estimation during flight ranging from over-predicting  $\text{VO}_2\text{peak}$  by 58% to under-predicting by 24% (personal communication with Dr. Alan Moore). To date, only one study has measured  $\text{VO}_2\text{peak}$  pre-, during, and post-flight using a metabolic gas analysis system. This study included 14 astronauts during ISS Increments 19-33 (April 2009 – November 2012). The results showed a mean decline in  $\text{VO}_2\text{peak}$  of 17% in the first two weeks of spaceflight followed by a trend upward throughout the remainder of the mission. Post-flight (24-28 h after landing)  $\text{VO}_2\text{peak}$  was reduced by ~15% from pre-flight and fully recovered 30 days after landing. Decrements in  $\text{VO}_2\text{peak}$  of these magnitudes could severely limit the astronauts' ability to efficiently perform mission-critical tasks, particularly in astronauts with low levels of pre-flight fitness. A subset of astronauts in this study who performed higher intensity aerobic exercise during flight maintained their pre-flight  $\text{VO}_2\text{peak}$ . Countermeasures to protect  $\text{VO}_2\text{peak}$  and accurate measurements of  $\text{VO}_2\text{peak}$  during the mission will be critical for mission success. Protection of  $\text{VO}_2\text{peak}$  may prove to be even more difficult during exploration missions where exercise equipment will be limited in volume and power capabilities and communication to the astronauts will likely be delayed and less frequent.

## **III. INTRODUCTION**

It is critical to protect aerobic fitness during long-duration spaceflight to maintain the crewmembers' capacity to perform long-duration activities and strenuous physical tasks that may

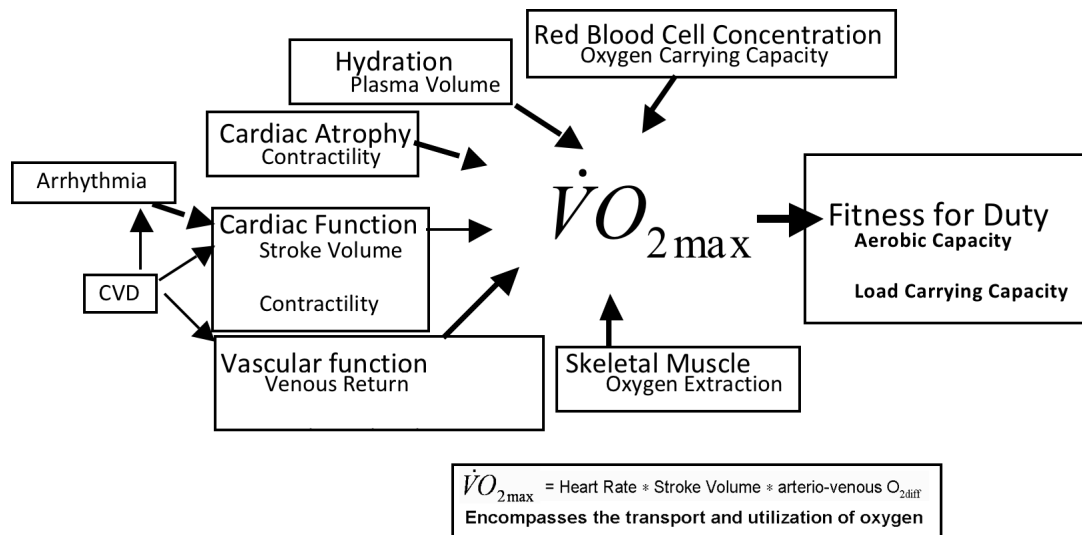
be required during extravehicular activities (EVAs) or emergency egress actions upon landing on Earth or during future exploration missions (Smith, Davis-Street et al. 2003, Kozlovskaya and Grigoriev 2004). In these scenarios, the crewmembers are required to perform activities under high levels of stress while wearing a space suit that restricts movement and is heavy when in a 1-G environment. For example, emergency egress tasks require normal ambulatory subjects to work at intensities at 85% of maximum heart rate (HR) (Bishop, Lee et al. 1999) and would be a much greater challenge after long-duration ISS missions that typically last 6 months or more. High-intensity EVA activity is not unprecedented; during lunar EVAs conducted during the Apollo era, there are several reports of EVAs performed at 78-85% of maximum HR (Portree and Trevino 1997). Although the precise plans regarding space exploration destinations are not well-defined, future exploration activities may require higher levels of aerobic fitness compared with the ISS EVA task requirements. Decrements in  $\text{VO}_2\text{peak}$  of 10% could severely limit the ability to perform activities requiring 85% of pre-flight  $\text{VO}_2\text{peak}$ .

$\text{VO}_2\text{peak}$  has only been measured during spaceflight in two studies due to concern of performing maximal exercise during spaceflight from the medical community and availability of metabolic gas analysis hardware during spaceflight. The first study to measure  $\text{VO}_2\text{peak}$  during spaceflight was conducted during short-duration (9-14 days) Space Shuttle missions (Levine, Lane et al. 1996), and the second was conducted more recently during long-duration (~4-6 months) ISS missions (Moore, Downs et al. 2014). Levine et al. found that Space Shuttle crewmembers experienced no significant decrease in  $\text{VO}_2\text{peak}$  during their mission, but  $\text{VO}_2\text{peak}$  was reduced by 22% immediately post-flight. Moore et al. recently reported a 17% decline in  $\text{VO}_2\text{peak}$  during the first two weeks of ISS missions that tended to increase during the mission but never fully returned to pre-flight levels.  $\text{VO}_2\text{peak}$  was reduced by 15% immediately (24-48 h) post-flight and returned to pre-flight levels by R+30. Most ISS astronauts (all except those participating in the Moore et al. study and an on-going in-flight exercise prescription study) performed submaximal exercise tests during flight. In agreement with Moore et al., results from long-duration in-flight *submaximal* exercise tests suggest that aerobic capacity is most impaired early in-flight, returns to near preflight levels at the end of ISS missions, and is again reduced significantly when tested 3-5 days after landing (Laughlin, Moore et al. 2003, Moore, Lee et al. 2003).

Factors that affect delivery of oxygen to the active muscles include HR, stroke volume (SV, the volume of blood expelled from the heart with each beat), cardiac output ( $Q_c$ , product of HR and SV), and extraction of oxygen from the arterial blood vessels by the muscles (measured as arterial-venous oxygen, a-v  $\text{O}_2$  difference) (Figure 1). The relationship between  $\text{VO}_2$ ,  $Q_c$ , and a-v  $\text{O}_2$  difference is quantified by the Fick equation (Rowell 1986):

$$\text{VO}_2 = Q_c \times \text{a-v } \text{O}_2 \text{ difference}$$

The early in-flight decline in  $\text{VO}_2\text{peak}$  is likely due to several factors, including time without exercise starting approximately 2 weeks prior to launch (due to availability of exercise equipment) and continuing up to 2 weeks after arrival at the ISS (due to schedule time constraints), space motion sickness, head-ward fluid shifts that cause a decrease in plasma volume, and changes in cardiac properties (e.g., reduced left ventricular mass and diastolic function) (Levine, Zuckerman et al. 1997, Perhonen, Franco et al. 2001, Narici and de Boer 2011). A reduction in plasma volume is the most rapidly occurring adaptation to spaceflight and bed rest and appears to have a strong influence on  $\text{VO}_2\text{peak}$ .



**Figure 1.** Diagram showing the major physiological contributors to VO<sub>2</sub>max.

In a review of previous investigations, Convertino reported that 70% of the variability in VO<sub>2</sub>peak following bed rest deconditioning can be explained by a decreased plasma volume (Convertino, Polet et al. 1997). Similarly, Stegemann et al. reported that decreased blood volumes were related to a decreased aerobic capacity after spaceflight (Stegemann, Hoffmann et al. 1997). Reduced circulating plasma volume may negatively affect exercise SV, the delivery of oxygen and nutrients to working muscle, and the removal of metabolic waste products. The persistent decrement in VO<sub>2</sub>peak throughout the mission is likely due to losses in muscle strength, cardiovascular function, and metabolic dysfunction. With exposures of at least 6 weeks to simulated microgravity (bed rest), structural changes in the myocardium (Perhonen, Franco et al. 2001) and the vasculature (Zhang 2001) may increasingly impair the delivery of oxygen to working muscles. Additionally, negative metabolic adaptations to simulated microgravity, such as reduced citrate synthase activity, become apparent after 4 weeks of unloading (Hikida, Gollnick et al. 1989, Berg, Tedner et al. 1993). Citrate synthase is the rate-limiting enzyme in the first step of the Krebs cycle; therefore, it plays a critical role in aerobic metabolism at the cellular level. Longer durations of spaceflight are associated with decreased muscle mass, strength, and endurance, which would be expected to impair aerobic exercise performance and decrease the efficacy of the muscle pump to protect venous return (Yang, Baker et al. 2007). The acute reductions in VO<sub>2</sub>peak (24-72 h upon return to Earth) are likely largely due to the above adaptations to spaceflight, as well as orthostatic intolerance.

Although most crewmembers experience reductions in VO<sub>2</sub>peak during and post-flight (Siconolfi, Charles et al. 1994, Greenisen, Hayes et al. 1999, Moore, Lee et al. 2001, Moore, Lee et al. 2003, Moore, Downs et al. 2014), exercise training studies in-flight and bed rest studies indicate that aerobic conditioning can be improved or at least maintained by performing daily resistance and aerobic exercise at a high intensity (Lee, Bennett et al. 1997, Lee, Schneider et al. 2005, Lee, Schneider et al. 2007, Lee, Schneider et al. 2009, Schneider, Lee et al. 2009, Ploutz-Snyder, Downs et al. 2014). The minimum exercise requirements required to maintain VO<sub>2</sub>peak at or near pre-flight levels is not known and will require a much larger data set to provide any recommendations regarding exercise prescriptions.

## **IV. EVIDENCE**

### **A. Spaceflight Evidence**

Most of the observations regarding aerobic capacity during and after spaceflight reviewed in this section are derived from experiences in the U.S. space program. Unfortunately, there have been few studies in either the U.S. or Russian programs that have actually measured maximum oxygen uptake ( $\text{VO}_{2\text{peak}}$ ) during or following spaceflight. The recent publication by Moore et al (2014) is the only study that has measured  $\text{VO}_{2\text{peak}}$  pre-, during, and post-flight in long-duration ISS crewmembers (Moore, Downs et al. 2014). Most spaceflight studies have used the HR response to submaximal exercise loads to make assumptions about changes in  $\text{VO}_{2\text{peak}}$ . This practice is based upon the general observation in ground-based studies that subjects will have a higher HR at a given absolute exercise intensity when they are not well-conditioned compared with the HR that would be observed following exercise training. However, as previously mentioned, this method of estimating changes in  $\text{VO}_{2\text{peak}}$  is not accurate and may lead to erroneous conclusions regarding changes in aerobic fitness and astronauts' ability to perform specific tasks.

#### **1. Program Era**

Exercise tests of aerobic fitness have been performed since the beginning of manned spaceflight. Early tests consisted of rudimentary evaluations of aerobic exercise tolerance. Over time, testing techniques and protocols were improved and have culminated with true measures of  $\text{VO}_{2\text{peak}}$  during the ISS era.

#### **a. Project Mercury**

The success of the sub-orbital flight of Alan B. Shepard in the Mercury space capsule "Freedom 7" on May 5, 1961, marked the beginning of manned exploration of space by the U.S. Project Mercury was conducted using small vehicles capable of holding only one occupant. These early flights were conducted to orbit a manned spacecraft around the earth, to investigate man's ability to function in space, and to demonstrate the successful recovery of both man and spacecraft safely. During the six flights of the Mercury program, two suborbital and four orbital, no studies of aerobic capacity were conducted. During the orbital flights, however, exercise tests were conducted in the spacecraft. Crewmembers performed a 30-second exercise session using a bungee cord with a 16-pound pull through a distance of 6 inches (White and Berry 1962). The crewmembers' HRs were increased during exercise and rapidly recovered afterward. These were the first demonstrations that the cardiovascular system is reactive to exercise during spaceflight.

Although exercise intolerance was not observed, in-flight exercise training was recommended for crewmember protection during future spaceflight missions. Specifically, the following quote was included in the post-mission report of the third U.S. manned orbital flight (Berry, Minners et al. 1962):

"An orthostatic rise in heart rate, fall in systolic blood pressure, and maintenance of the diastolic pressure was noted during the 24 hours immediately after landing. Such a hemodynamic phenomenon may have more serious implications for a longer mission. A prescribed in-flight exercise program may be necessary to



preclude symptoms in case of the need for an emergency egress soon after landing.”

This statement indicates that exercise was being considered by NASA as a possible countermeasure for spaceflight exposure as early as 1962.

#### **b. Project Gemini**

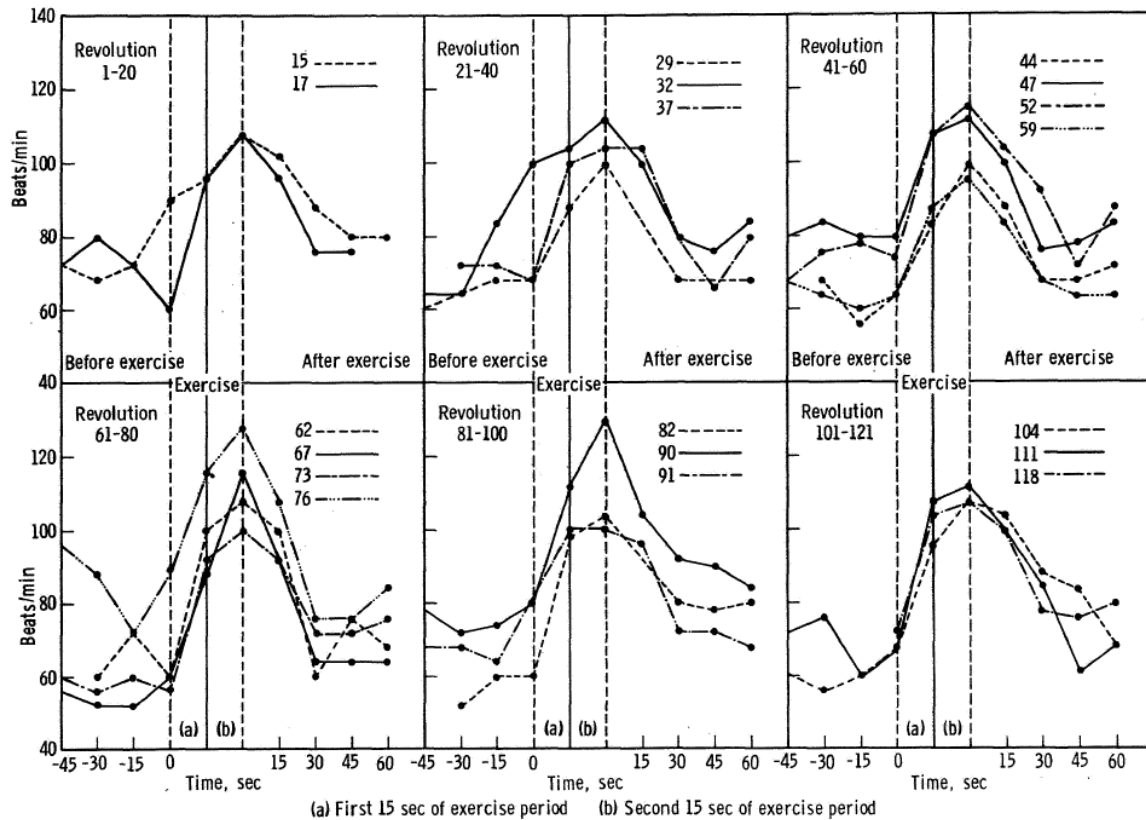
The Gemini project was conducted from 1964-1966 using two-man space capsules launched into orbit atop modified U.S. Air Force Titan-II intercontinental ballistic missiles. These flights were conducted to gain experience necessary to conduct future missions to the moon. Therefore, the objectives of these flights were to subject man and equipment to the spaceflight environment for periods lasting up to 2 weeks, to practice docking and rendezvous with orbiting target vehicles, and to refine the landing methodology. There were 12 Gemini flights: 2 unmanned and 10 flights with 2-person crews.

During three of the manned flights (Gemini IV-4 days, Gemini V-7 days, and Gemini VII-14 days), exercise testing was conducted as part of an experiment designated as M003 – In-flight Exercise and Work Tolerance (Berry and Catterson 1967). These tests consisted of crewmembers performing 30-second exercise sessions with a bungee pull device (Figure 2). The target rate of pulling was one pull per second, and the device delivered a force of 70 lbs (31.8 kg) at full extension. HR and blood pressure were measured during these tests, which were conducted several times during each of the missions.



**Figure 2.** Gemini in-flight exerciser (Dietlein and Rapp 1966).

The HR response of the crewmembers to the brief exercise session remained relatively constant within an individual throughout the flights [Figure 3, (Dietlein and Rapp 1966)]. The investigators suggested that these results indicated there were no decrements in the physical condition of the crews during flights of up to 14 days. The workloads imposed by this test were relatively mild and the testing time duration was brief; therefore, it is likely this test was not a specific or sensitive measure of aerobic capacity.



**Figure 3.** Example of Gemini in-flight exerciser data from a single crewmember (Berry and Catterson 1967).

Additionally, the first pre- and post-flight graded exercise tests were performed by six crewmembers from four of the Gemini flights to determine the effects of microgravity on post-flight performance (Dietlein and Rapp 1966, Berry and Catterson 1967). The test protocol was conducted on an electronic cycle ergometer on which the crewmember pedaled at 60-70 rpm. The work rate was set initially at 50 Watts for 3 minutes and increased by 15 Watts each minute until the crewmember's HR reached  $180 \text{ beats} \cdot \text{min}^{-1}$ . The data from these tests were never published in a comprehensive manner, but in the NASA Gemini Summary Conference Report (Berry and Catterson 1967), it was reported that all but one of the crewmembers tested experienced a decrease in exercise capacity. Decline in exercise capacity was demonstrated by an increase in the HR response to exercise and a reduction in  $\text{VO}_2$  at exercise termination. For example, the  $\text{VO}_2$  at test termination was 19% and 26% lower after flight in the 2 crewmembers of Gemini VII (Dietlein and Rapp 1966). Figure 4 is an illustration of the graded exercise test results of a Gemini IX crewmember (Berry and Catterson 1967). Although these were not true measurements of  $\text{VO}_{2\text{peak}}$ , the investigators suggested that these data provide strong evidence that aerobic capacity was compromised following the Gemini flights. The pre- to post-flight decline in  $\text{VO}_2$  at test termination was suggested to have been related to decreased total blood volume (reduced in 5 of 6 crewmembers examined), plasma volume (decreased in 4 of 6), and red cell mass (decreased in all 6 crewmembers). The factors that were speculated to have caused these hematological changes were hyperoxia (the Gemini spacecraft environment was 100% oxygen at 5 psia, or 259 mmHg), physical confinement of the crew, dietary factors, and weightlessness.

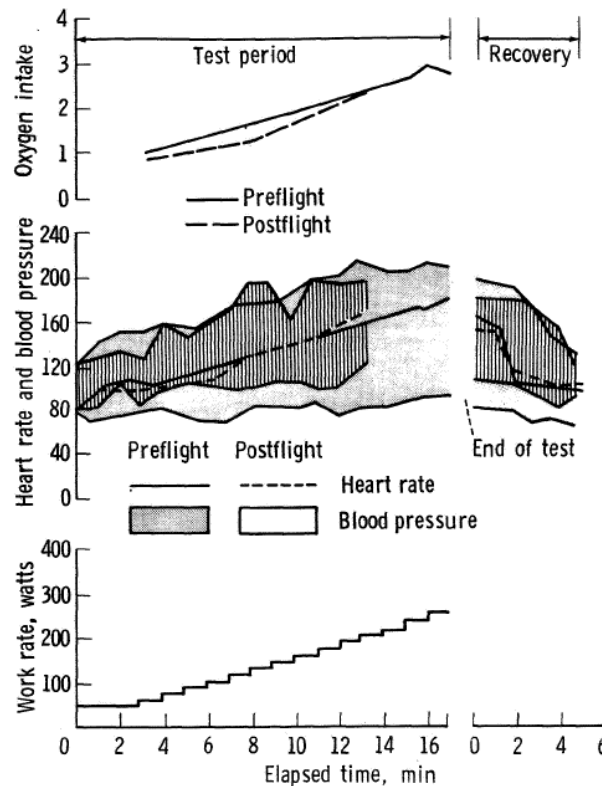


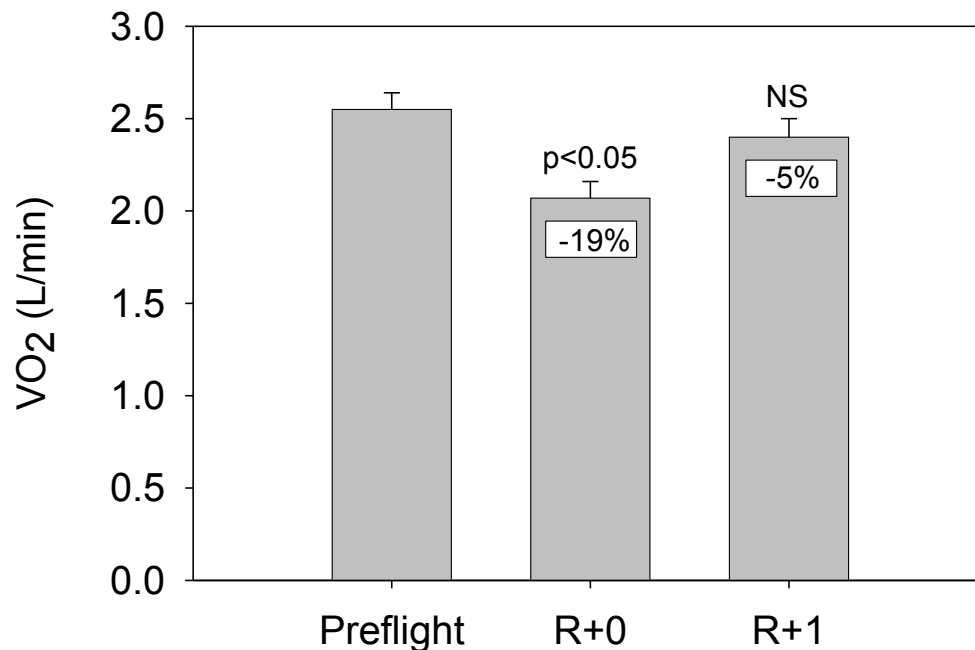
Figure 4. Gemini IX pre- and post-flight exercise test results (Berry and Catterson 1967).

### c. Apollo Program

The Apollo program is best remembered for the flight of Apollo 11, which was the first manned exploration of the moon. The Apollo program consisted of 11 flights conducted between 1968 and 1972. Of these flights, six delivered astronauts to the lunar surface. The Apollo crews consisted of 3 men per flight, and the flight durations ranged from 5.9 to 12.7 days.

The crews of Apollo 7-11 and 14-17 ( $n=27$ ) participated in submaximal exercise testing to quantify pre- to post-flight changes in the physiological response to exercise (Berry 1970, Rummel, Michel et al. 1973, Rummel, Sawin et al. 1975, Rummell, Sawin et al. 1975). An electronically braked cycle ergometer was used for exercise testing, with work rate controlled using a HR feed-back loop.  $\text{VO}_2$  was also measured during these exercise tests. The test protocol consisted of 3 exercise work rates that produced HRs of 120, 140, and 160  $\text{beats}\cdot\text{min}^{-1}$ . The Apollo 9 and 10 crews also performed an additional exercise stage that elicited a HR of 180  $\text{beats}\cdot\text{min}^{-1}$ . The  $\text{VO}_2$  at all exercise stages was significantly less on landing day (R+0), but was near pre-flight levels 24-26 h following landing (R+1; Figure 5). Exercise  $\text{Q}_c$  measurements were also obtained from the crews of Apollo 15-17.  $\text{Q}_c$  was 37% lower on R+0 than it was before flight, and SV was reduced from  $145 \pm 34 \text{ ml}\cdot\text{beat}^{-1}$  to  $92 \pm 34 \text{ ml}\cdot\text{beat}^{-1}$ . On R+1, SV was only 7% lower (not statistically different) than pre-flight. The mean pre- to post-flight change in plasma volume of the Apollo astronauts was  $-4.4 \pm 1.7\%$  on R+0 and  $+4.8 \pm 2.2\%$  on R+1 (Leach, Alexander et al. 1975). The rapid normalization of the crewmembers' responses to

exercise suggests that changes in plasma volume played a role in the post-flight decline in  $\text{VO}_2$  on R+0 at the terminating workload.



**Figure 5.**  $\text{VO}_2$  changes at an exercise stage eliciting a HR of 160 beats/min (Apollo crews  $n=27$ ).

#### **d. Skylab Program**

The Skylab program was the first U.S. space station and the first experience with longer duration spaceflight. The station was launched in May 1973 atop a Saturn V vehicle, the last launch of the rocket that first took man to the moon. Three crews traveled to Skylab using Apollo-era command modules launched on Saturn 1B vehicles. The mission durations were 28 days (Skylab 2), 59 days (Skylab 3), and 84 days (Skylab 4). Medical activities accounted for approximately 7% of the mission time during flight.

The Skylab missions marked the first time metabolic gas analysis hardware was available for use in-flight. The Skylab metabolic gas analyzer was described in detail by Michel et al. (Michel, Rummel et al. 1975). During the Skylab missions, routine submaximal graded exercise testing was performed on a cycle ergometer, and expired metabolic gasses were analyzed to determine  $\text{VO}_2$  (Michel, Rummel et al. 1975, Michel, Rummel et al. 1977) (Figure 6). The submaximal exercise consisted of 5-minute stages of rest followed by exercise at work rates eliciting 25%, 50%, 75%, and 25% of pre-flight  $\text{VO}_{2\text{peak}}$ . Pre-flight  $\text{VO}_{2\text{peak}}$  was established during previous graded exercise tests to volitional fatigue conducted one year (L-360) and 6 months (L-180) prior to launch. The submaximal exercise test was repeated approximately every 6 days during each flight, starting with flight day 6. The in-flight HR response to submaximal exercise did not change during the mission, which was taken as an indicator of no change in the aerobic fitness of the crews. Cardiac output ( $Q_c$ ) was not measured during flight, but it was measured during the exercise tests performed before and several times following flight (Buderer,

Rummel et al. 1976). The mean  $Q_c$  of all crewmembers at the 75% work stage was decreased by approximately 30% and SV was decreased by 50% on R+0. Within 10 days after landing,  $Q_c$  and SV were within 10% of pre-flight values, but complete recovery was not noted until 31 days following flight. The HR response to exercise was markedly elevated immediately following flight and gradually returned to pre-flight levels by R+24 days. Plasma volume declined by 12.5% on R+0 and returned to pre-flight values by R+14 days (Johnson, Driscoll et al. 1977). These changes did not appear to be related to mission duration. Although  $VO_{2peak}$  was not measured in these subjects, the post-flight exercise responses were assumed to be consistent, with a decrease in aerobic capacity during the early recovery period and a gradual return to pre-flight levels over the month following flight.

An attempt was made to collect  $VO_{2peak}$  data during instrumented personal exercise sessions to near-maximum exercise levels on four crewmembers of the Skylab 3 and 4 missions (Sawin, Rummel et al. 1975). However, a number of problems prevented accurate measurement of  $VO_{2peak}$ . The Skylab cycle ergometer was limited to a work rate of 286 Watts, and 3 of the 4 crewmembers were able to exceed this work rate during pre-flight testing. Therefore, these 3 crewmembers performed prolonged work at 286 Watts during flight to elicit a “maximum effort.” The limiting factor for these sessions was leg fatigue, rather than a true cardiovascular maximum effort. The device that measured expired ventilation (a component of the measurement of  $VO_2$ ) could only accurately measure values up to  $150 \text{ L} \cdot \text{min}^{-1}$ , and this level was exceeded in several tests, possibly because of the low cabin pressure of Skylab (259 mmHg). The investigators concluded that the  $VO_{2peak}$  of the crewmembers was likely maintained and perhaps even increased during flight, although the measurement hardware limitations greatly hinder the interpretation of the data.

Changes in thermoregulatory control may be impacted during and after spaceflight. Leach et al. reported that evaporative water loss was reduced by an average of 11% in 9 Skylab crewmembers during their in-flight exercise compared with pre-flight (Leach, Alfrey et al. 1996). The authors suggested that the sweating responses may have been reduced in the microgravity environment through the formation of a film of sweat on the surface of the skin because of reduced sweat dripping, which impaired air flow across the skin and sweat evaporation. Furthermore, reduced gravity would have impaired spontaneous convection, in which air rises or falls due to differences in density, and low air flow in the cabin of space vehicles during spaceflight may limit heat loss capacity (Fortney 1991, Novak 1991).

Fortney et al. observed that the thermoregulatory mechanisms were impaired in two crewmembers when performing exercise following long-duration spaceflight (115 days) onboard the Mir space station. Both crewmembers had a mildly elevated core temperature at rest and after 20 min of exercise at 40%  $VO_{2peak}$ , and they had a delayed onset of the sweating rate response and skin vasodilation. Neither crewmember was allowed to complete the second exercise stage post-flight (20 minutes at 65% pre-flight  $VO_{2peak}$ ) because the flight surgeon terminated the test “due to an excessive rise in HR” (Fortney, Mikhaylov et al. 1998). Despite the shortened exercise time, both crewmembers had a core temperature at the end of the post-flight exercise bout similar to the core temperature at the end of the entire exercise protocol during pre-flight testing. Both crewmembers exhibited lower skin blood flow and sweating rate responses, which may have contributed to this elevated core temperature.



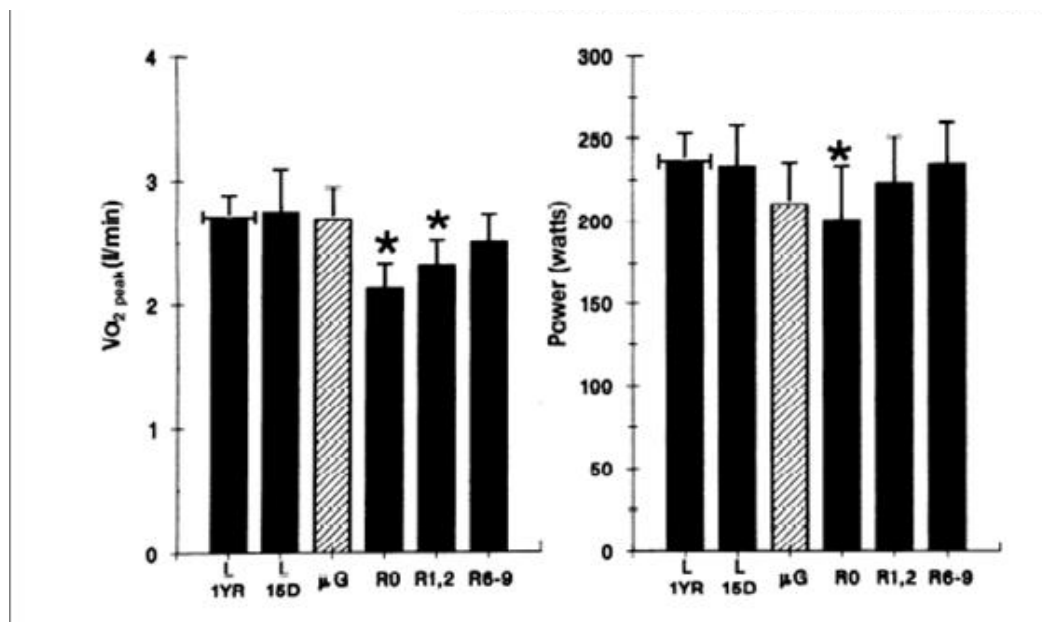
**Figure 6.** Skylab crewmember performing cycle exercise test with  $\text{VO}_2$  measurements.

#### **e. Space Shuttle Program**

The first launch of the Space Shuttle program was in April 1981. The Space Shuttle is unique in that it is the first winged space vehicle that is designed to be launched from the ground and return to Earth to be reused. There have been five Shuttle orbiters, two of which were destroyed – one during launch (*Challenger*, January 1986) and the other during deorbit operations (*Columbia*, January 2003). The payload capacity of the Space Shuttle is considerable (22,700 Kg mass and 1,106 m<sup>3</sup> volume). Five to seven astronauts typically flew on a Space Shuttle mission. The intended use of the Space Shuttle from its inception was to support the future space station; however, for the majority of the Space Shuttle program, the vehicle was used to transport large payloads into orbit (such as the Hubble Space Telescope) and to conduct other low-Earth orbit operations. The Space Shuttle cargo bay was also used to carry a laboratory, such as the Spacelab and SPACEHAB™ modules, in which human life sciences experiments have been conducted.

The first studies to actually measure  $\text{VO}_{2\text{peak}}$  prior to, during, and immediately following spaceflight were conducted during the Space Shuttle era. Of these, only one study measured  $\text{VO}_{2\text{peak}}$  during spaceflight. Levine and co-workers reported the results of the peak cycle ergometer tests on six astronauts during the Spacelab Life Sciences (SLS)-1 (9 day) and SLS-2 (14 day) missions (Levine, Lane et al. 1996).  $\text{VO}_{2\text{peak}}$  measured between flight day 5 and 8 was not different than pre-flight  $\text{VO}_{2\text{peak}}$ . Interestingly, submaximal  $\dot{Q}_c$  (measured on the same astronauts and same days on which  $\text{VO}_{2\text{peak}}$  was reported in the Levine study) was lower during spaceflight (Shykoff, Farhi et al. 1996). Shykoff et al. speculated that either the  $\dot{Q}_c$  needed to support moderate to heavy exercise is less in microgravity than on the ground or that a reduction in circulating blood volume caused by the storage of blood in the pulmonary circulation limited the increase in  $\dot{Q}_c$  by reducing the SV (Shykoff, Farhi et al. 1996). Reduced submaximal  $\dot{Q}_c$  during spaceflight is difficult to reconcile with the observation that  $\text{VO}_{2\text{peak}}$  did not change

during flight in these subjects. Of additional note, Alfrey and co-workers reported that plasma volume was reduced by 17% on flight day (FD) 1 and 12% on FDs 8-12 during these spaceflights (Alfrey, Udden et al. 1996). At this point, the decrease in  $Q_c$  without a corresponding change in  $VO_{2peak}$  observed in the Shykoff study cannot be explained. On landing day, subjects experienced a mean reduction in  $VO_{2peak}$  and  $Q_c$  of 22% and 24%, respectively, with no change in maximum HR. Levine and colleagues concluded that the post-flight reduction in maximum  $Q_c$ , and thereby  $VO_{2peak}$ , was due entirely to changes in SV (Levine, Lane et al. 1996). The reduction in SV was likely due to impaired venous return caused by a decrease in plasma volume, which remained depressed on the first recovery day (Alfrey, Udden et al. 1996, Levine, Lane et al. 1996).  $VO_{2peak}$  recovered by approximately 50% on R+1-2 and had fully recovered to preflight levels by R+6-9 (Figure 7) (Levine, Lane et al. 1996). Plasma volume had recovered to preflight values on R+6 (Alfrey, Udden et al. 1996).



**Figure 7.**  $VO_2$  max was not changed during the SLS-1 and SLS-2 flights; however, it decreased in the first 2 days following flight (Levine, Lane et al. 1996).

Moore et al. (Moore, Lee et al. 2001) conducted a study to determine whether maximal exercise performed on the last day of flight would preserve post-flight orthostatic function and aerobic capacity, as suggested by a previous bed rest study (Convertino 1987). Astronauts (n=8) participating in flights ranging from 8-14 days in duration performed a peak cycle ergometer test before flight, on the last full flight day, and post-flight on R+0, R+3, and R+14. Although  $VO_2$  was not measured during flight, the peak HR and the peak work rate during the in-flight tests were not different from pre-flight levels. Both of these observations suggest that  $VO_{2max}$  was unchanged during flight. However, when  $VO_2$  was measured during exercise testing on landing day, the crewmembers experienced a decline in  $VO_{2peak}$  ranging from 11-28% (mean decline 18%). Three days following flight,  $VO_{2peak}$  was still reduced by an average of 11% but returned to baseline values by R+14. Similar to the findings of Levine et al. (Levine, Lane et al. 1996), maximum HR did not change following flight; thus, it is likely that reductions in  $Q_c$  and SV played a role in the decrease in  $VO_{2peak}$  on R+0 and R+3.



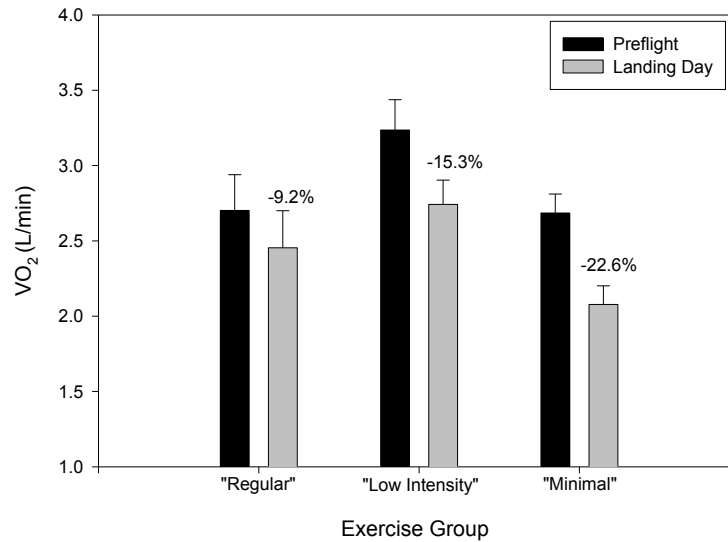
In contrast to the above studies, Trappe et al. (Trappe, Trappe et al. 2006) reported results consistent with aerobic deconditioning during a Space Shuttle flight. In this study, 4 astronauts on the 16-day STS-78 flight performed in-flight and post-flight (R+4) exercise tests with a workload equivalent to 85% of pre-flight  $\text{VO}_{2\text{peak}}$ . A mean increase of 7% in exercise HR at the 85% workload was reported on FD 8, and a 9% increase was reported on FD 13, which was interpreted as a sign of aerobic deconditioning. The reason for differences between these results and those reported by Levine and Moore are not readily explainable, but they may have been related to differences in the pre-flight fitness levels of the crewmembers participating in the studies [Trappe et al.:  $3.59 \text{ l}\cdot\text{min}^{-1}$ , Moore et al.:  $3.29 \text{ l}\cdot\text{min}^{-1}$ , Levine et al.:  $2.76 \text{ l}\cdot\text{min}^{-1}$ ], exercise countermeasures and other physical testing performed during the flights, or individual differences in the response to spaceflight (e.g., degree of space motion sickness, medications used). Although  $\text{Q}_c$  and SV were not measured in the study reported by Trappe et al., it is possible that submaximal HRs were increased as a compensatory response to a decrease in SV. On R+4 and R+8,  $\text{VO}_{2\text{peak}}$  was reduced by 10.3% and 5.0%, respectively. This finding follows the general trend of recovery in  $\text{VO}_{2\text{peak}}$  observed by both Levine et al. and Moore et al.

Investigations related to exercise capacity and the preservation of the cardiovascular responses to exercise were conducted by NASA during the Extended Duration Orbiter Medical Project (EDOMP) from 1989 to 1995. These studies were: 1) designed to be relevant to spaceflight operations; 2) required to be related to performance of the crewmembers during entry, landing, or egress from the Space Shuttle; and 3) conducted as NASA Detailed Supplemental Objectives (DSOs). DSO studies are limited in the amount of hardware stowage that can be used to support the studies during flight; therefore, the majority of these involved pre- vs. post-flight comparisons. In addition, fairly early in EDOMP, NASA's Committee for the Protection of Human Subjects limited the intensity of exercise investigations during and immediately following spaceflight to levels of no greater than 85% of pre-flight  $\text{VO}_{2\text{peak}}$ . The authors of this report are not aware of any cardiovascular anomaly that occurred either during or following flight that precipitated this exercise limitation. In any event, this restriction is the reason for the limitation of exercise intensity of the subjects of Trappe et al. and subsequent investigations. Despite the above-listed limitations, studies conducted during the EDOMP era produced findings related to the spaceflight-induced decrease in aerobic capacity. One study examined the effects of continuous vs. low-level interval exercise on post-flight aerobic capacity (Siconolfi, Charles et al. 1994). During flight, the astronauts ( $n=17$ ) performed either continuous exercise or interval exercise on a small passive treadmill or served as controls (Figure 8). HR was used by the exercising crewmembers to regulate exercise intensity. Treadmill testing to measure  $\text{VO}_{2\text{peak}}$  was performed before and 2 days following flight.  $\text{VO}_{2\text{peak}}$  was maintained in both exercise groups, while the control subjects experienced a 9.5% loss (Siconolfi, Charles et al. 1994). Although this study did not measure  $\text{VO}_{2\text{peak}}$  immediately following flight, it demonstrated that  $\text{VO}_{2\text{peak}}$  following flight could be altered by in-flight training.



**Figure 8.** Astronauts exercising on passive space shuttle treadmill and the shuttle cycle ergometer.

Another study conducted during EDOMP was designed to monitor aerobic exercise performed during flight and the influence of this exercise on the HR and  $\text{VO}_2$  responses to exercise testing following flight (Greenisen, Hayes et al. 1999). Astronauts ( $n=35$ ) performed incremental (50 Watts for 3 minutes, followed by a 50-Watt increase every 3 minutes) upright cycle ergometer exercise tests with  $\text{VO}_2$  and HR measurements prior to flight (L-10) and on landing day (R+0). These tests were terminated at the work stage that elicited 85% of each participant's age-predicted maximum HR;  $\text{VO}_2$  was not measured. Exercise countermeasures for use during flight were not prescribed, but each astronaut wore a HR monitor that recorded both the HR and duration of their exercise sessions. Most exercise sessions were completed on the Space Shuttle cycle ergometer (a treadmill was only available on one mission) (Figure 8). The major finding of the study was that astronauts who performed regular aerobic exercise during flight demonstrated a smaller elevation in HR at the termination workload compared with astronauts who exercised less frequently or at a lower intensity (Figure 9). Regular aerobic exercise was defined as three or more sessions per week, with each session lasting at least 20 minutes and at an intensity that elicited a HR of  $> 70\%$  of their age-predicted maximum HR (Greenisen, Hayes et al. 1999).  $\text{Q}_c$  was not measured in these subjects, but the relative tachycardia experienced by the crewmembers on landing day is consistent with compensation for a decreased SV. Although speculative, it is possible that plasma volume was better maintained in the "regular exercise" subjects. Lee and co-workers, who reported on the R+0 stand test findings of these subjects (Lee, Moore et al. 1999), observed a greater HR response and reduced pulse pressure (often used as an index of SV) during standing in the "minimal" exercise subjects. Thus, it appears that, at least for Shuttle-duration flights, a decline in  $\text{VO}_{2\text{peak}}$  immediately following flight may be partially attenuated by exercise conducted during flight.



**Figure 9.** Oxygen consumption achieved at 85% of the age-predicted maximum HR pre- and post-flight in crewmembers (n=35) who participated in different amounts of in-flight exercise.

"Regular" (n=11) - Exercised > 3x/week, HR > 70% age-predicted, > 20 min/session

"Low Intensity" (n= 10) - Exercised > 3x/week, HR < 70% age-predicted, > 20 min/session

"Minimal" (n=14) - Exercised < 3x/week, HR and min/session variable. Redrawn from Greenisen et al. (Greenisen, Hayes et al. 1999).

#### f. International Space Station (ISS)

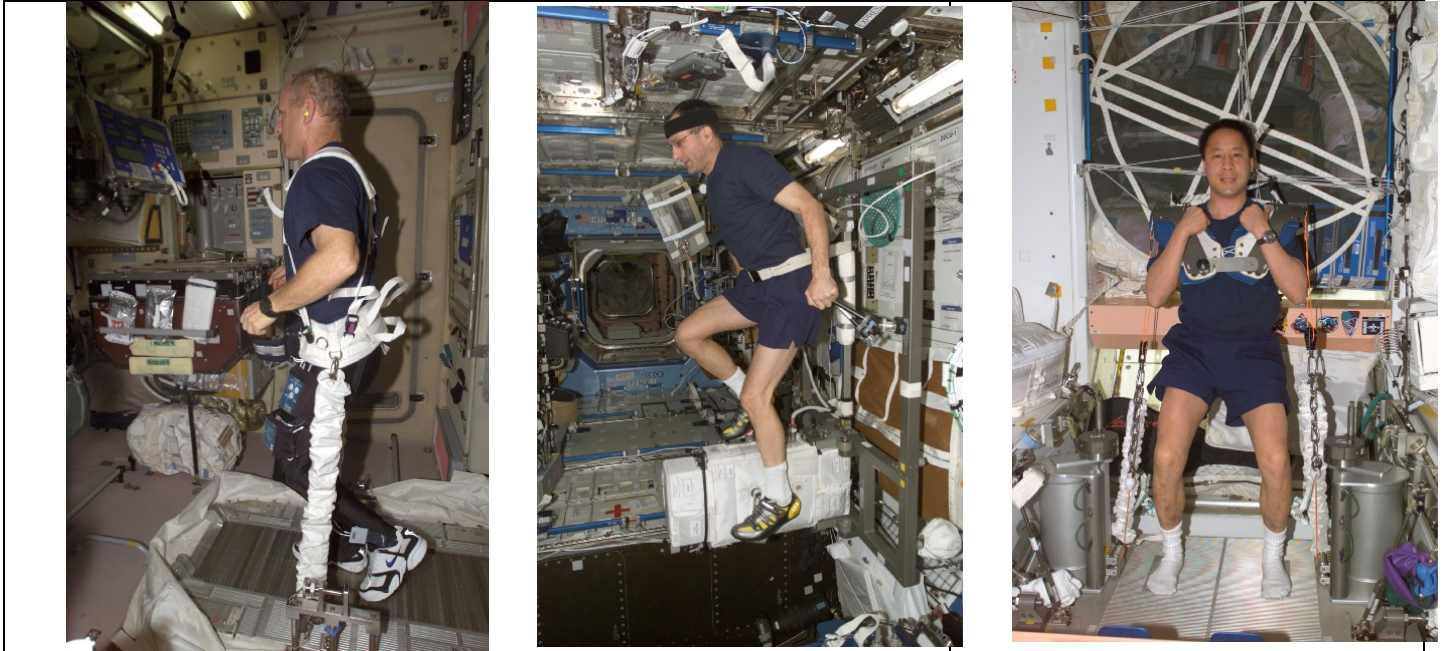
The ISS is a low-Earth orbiting research facility. ISS assembly in space was initiated in 1998, and a manned presence on board ISS has continued since November 2000. The crews of the ISS have been comprised of U.S., Russian, European Space Agency (ESA), Canadian Space Agency (CSA), and Japanese Exploration Agency (JAXA) astronauts. The crew size for ISS Expeditions has varied between two and six long-duration occupants. Supplies and crewmembers are currently ferried to and from ISS on the Russian Soyuz vehicle. The U.S. Space Shuttle also carried astronauts to and from the ISS until its retirement in 2011. A number of different unmanned cargo vehicles deliver supplies to the ISS. To date, there have been 39 long-duration expeditions with average mission lengths of 4-6 months. A year-long mission is planned for 2015.

***ISS Exercise Hardware and Prescription.*** ISS crewmembers perform treadmill, cycle ergometer, and resistive exercise during their missions to counter the effects of long-duration spaceflight exposure on muscle, bone, and cardiovascular fitness (Figure 10). Exercise sessions with a total duration of 2.5 h are scheduled each day. This period includes the time needed to change into exercise clothing and clean up following activity, so the effective daily exercise time is approximately 1 hour and 15 minutes. Typically, crewmembers perform aerobic and resistance exercise 6 days per week; however, the exercise prescriptions and adherence to the prescriptions have varied widely between crewmembers. The Astronaut Strength, Conditioning, and Rehabilitation (ASCR) group has worked in more recent missions toward standardizing exercise prescriptions.

Exercise equipment and equipment availability have varied throughout the history of the ISS. For example, there have been times when the crewmembers were not able to exercise due to

hardware failure or were only able to exercise at lower intensities to conserve station power resources. The ISS was recently outfitted with a new suite of exercise hardware that provides the ability to exercise at higher intensities with improved instrumentation for data monitoring and downlinking capabilities. Historically, exercise data were not well tracked due to poor HR data quality or sporadic use of the HR monitor by the crewmembers, as well as difficulty with syncing the data from the exercise devices to the HR data. However, exercise data reporting has been greatly improved over the last several years due to the improved quality of HR data (although significant dropout still occurs) and because the new suite of exercise hardware is instrumented to record exercise loads and speeds. These improvements allow researchers and the NASA medical community to more accurately monitor the astronauts' adherence to the exercise prescriptions and track progressions in performance during the mission. These efforts will provide a greater understanding of the in-flight exercise intensity and volume requirements needed for maintaining aerobic fitness.

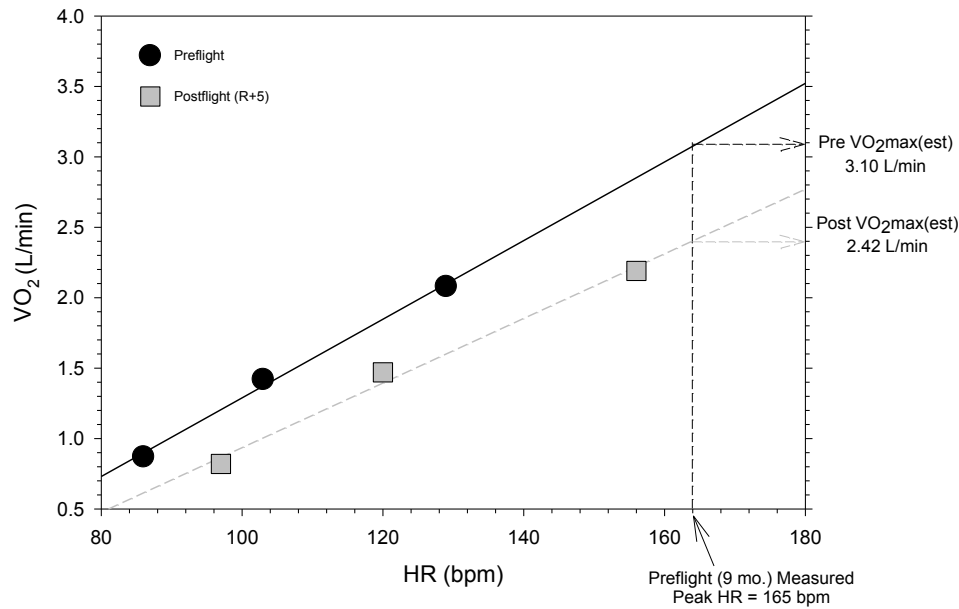
The interim Resistive Exercise Device (iRED) was replaced with the Advanced Resistance Exercise Device (ARED) in 2008. The ARED provides a significant improvement from the iRED in both maximum loading capabilities and loading characteristics. The ARED can provide concentric loading up to 600 lbs, an eccentric-concentric ratio of ~90%, and constant force throughout the range of motion using inertial flywheels. In comparison, the iRED was limited to 300 lbs and an eccentric to concentric ratio of only 60-80%, and the load was not constant throughout the range of motion (Lee, Shackelford et al. 2004). More detailed information on the iRED and ARED can be found in (2014). The first-generation ISS treadmill, Treadmill with Vibration Isolation System (TVIS), was replaced in 2010 by the Combined Operational Load Bearing External Resistance Treadmill (COLBERT), technically named the Treadmill 2 (T2). The T2 allows astronauts to run up to 12 mph (the TVIS was limited to 6-7 mph) with higher percentages of body weight loading due to improvements in the harness comfort. Astronauts have used both the TVIS and T2 in the non-motorized and motorized modes. The Cycle Ergometer with Vibration Isolation System (CEVIS) is capable of exercise loads from 25-350 Watts (controllable to 1-Watt increments) and also allows stable work rates to be applied between pedaling rates of 50-120 rpm.



**Figure 10.** International Space Station crewmembers exercising on the treadmill with vibration isolation system (left), the cycle ergometer (center), and the interim resistive exercise device (right).

***Aerobic Exercise Testing.*** Aerobic testing performed on an upright cycle ergometer (Excalibur Sport™, Lode BV, Groningen, Nederland) has been performed on U.S., ESA, CSA, and JAXA crewmembers as a medical requirement before and after all but the first ISS mission; in-flight testing has been performed using the CEVIS. Testing to establish pre-flight  $\text{VO}_{2\text{peak}}$  and peak HR is performed by each crewmember approximately 9 months to 1 year before flight. Historically, a submaximal test protocol was performed 60 days before launch (L-60), flight day (FD) 15, every 30 FDs following the initial in-flight test, and 5 and 30 days after landing (R+5 and R+30). The submaximal testing protocol consists of four five-minute stages at workloads equivalent to 25%, 50%, 75%, and 25% of pre-flight  $\text{VO}_{2\text{peak}}$ . Starting with Expedition 36, the medical requirement changed to perform maximal cycle tests pre- and post-flight and submaximal tests in-flight. Pre- and post-flight maximal and submaximal tests are performed with  $\text{VO}_2$  measurements, but in-flight tests use only HR monitoring (via ECG and a separate HR monitor) because technical and budgetary issues prevented a metabolic gas analysis system from being flown until the installation of the portable pulmonary function metabolic gas analysis (PPFS) system during Expedition 19.

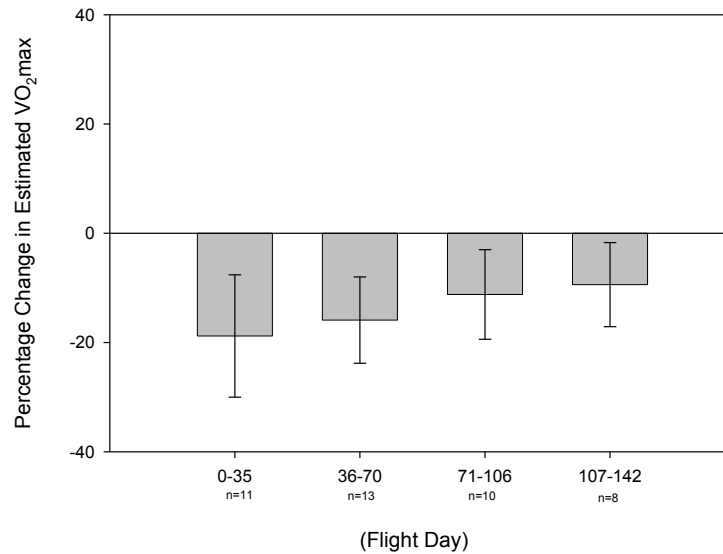
***Only one published study has measured  $\text{VO}_{2\text{peak}}$  pre-, in-, and post-flight (Moore, Downs et al. 2014) during ISS missions.***



**Figure 11.** Linear extrapolation method of estimating  $\text{VO}_2\text{max}$ . The illustrated data are from an ISS crewmember.

**Submaximal Test Results.** The HR data obtained during the in-flight tests and the  $\text{VO}_2$  data obtained during the pre-flight tests are used (this assumes no change in the metabolic cost of cycle exercise during flight) to estimate  $\text{VO}_2\text{peak}$  using a linear extrapolation method (Figure 11) from the submaximal data. This method is commonly used during field testing of subjects and is a good predictor of mean  $\text{VO}_2\text{peak}$  of a group (2003, 2009), but it is not an accurate measure of individual  $\text{VO}_2\text{peak}$  (Lee, Moore et al. 1993). In fact, this estimation method has resulted in errors ranging from 58% over-prediction to 24% under-prediction of  $\text{VO}_2\text{peak}$  compared with measured values (personal communication from Dr. Alan Moore). These errors in estimation are likely due to microgravity-induced hypovolemia (elevates the HR response to exercise during flight) and difference in the metabolic cost of exercising in 1-G vs. 0-G. Data collected from ISS astronauts indicate that submaximal  $\text{VO}_2$  measured in-flight is slightly lower than preflight values (Dr. Alan Moore, personal communication). Although the reason for this difference in metabolic cost is not known, differences in cycling posture between 1-G and ISS and the hard mounted 1-G bike compared with the CEVIS vibration isolation system are likely important factors.

Although the submaximal data cannot be used to accurately quantify changes in astronauts' fitness levels during flight, they are the only data available on the cardiovascular response to exercise of most crewmembers. Submaximal cycle ergometer tests showed an elevated HR response during flight, indicating that estimated  $\text{VO}_2\text{peak}$  was reduced by an average of 19% (Figure 12). Some recovery (lowering) of the HR response to the same absolute exercise work rates occurs throughout flight, and the estimated  $\text{VO}_2\text{peak}$  is typically recovered to within 10% of pre-flight values later during the missions. These data differ from that reported during the Skylab era when the HR response to exercise during flight did not differ from pre-flight values.



**Figure 12.** Percentage change in  $\text{VO}_2\text{peak}$  during ISS flights, estimated from changes in the HR response during submaximal exercise tests. Data from unpublished ISS medical testing.

Post-flight  $\text{VO}_2$  measured during the submaximal exercise tests are not different than pre-flight values, but the HR response to the same absolute exercise work rate is elevated on R+5. Plasma volume is normalized to pre-flight levels by R+5 (Dr. Steven Platts, personal communication); therefore, the elevation in HR may be due to a combination of lowered erythrocyte mass and muscular detraining. The ISS crewmembers' estimated  $\text{VO}_2\text{peak}$  values on R+5 decline an average of 16% from pre-flight values (Figure 13), which is similar to the actual  $\text{VO}_2\text{peak}$  change on R+0 during Space Shuttle flights (Levine, Lane et al. 1996, Moore, Lee et al. 2001) but is greater than the deconditioning measured between R+1 and R+9 in Shuttle crewmembers (Trappe, Trappe et al. 2006). It is likely that the Shuttle crew members were experiencing orthostatic intolerance or reduced plasma volume that resulted in the R+0 decrease but had recovered these cardiovascular parameters within 24-48 h. Together, these results suggest that the deconditioning experienced by ISS crewmembers is greater or lasts longer than that experienced by Space Shuttle crews. The HR response to exercise is not different than the pre-flight response by R+30; therefore, it is assumed that  $\text{VO}_2\text{peak}$  is recovered in ISS crewmembers by this time.



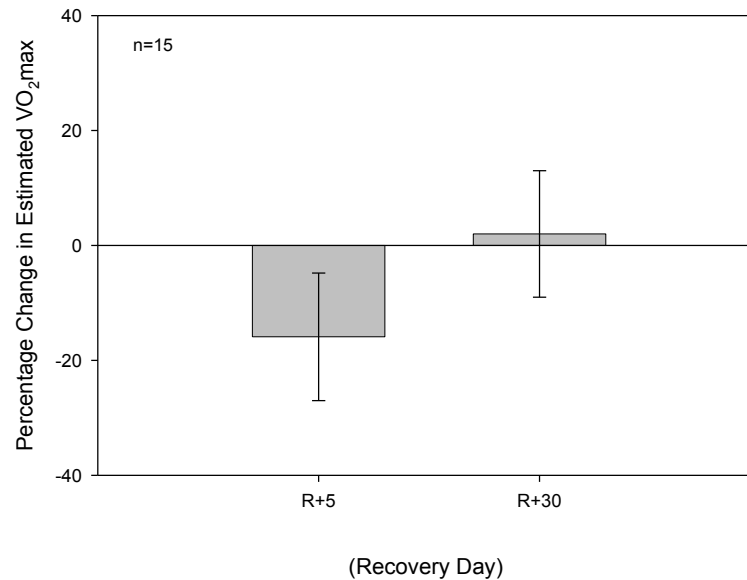


Figure 13. Percentage change in estimated  $\text{VO}_{2\text{peak}}$  following ISS flights.  
Data from ISS medical testing via LSAH.

The Russian cardiovascular exercise test data from four cosmonauts during ISS flights are remarkably similar to that observed in the U.S. tests reported above (Popov, Khusnutdinova et al. 2004). Russian cosmonauts perform a cycle test, designated as MO-3, on the veloergometer every 30 days during flight. This test is conducted using 3-minute stages at 125, 150, and 175 Watts. The HR response to exercise of these cosmonauts was greatest during the test that was performed 1 month into flight and became progressively lower as the flight duration increased. This response is consistent with an initial decline and recovery of  $\text{VO}_{2\text{peak}}$  during flight. The authors of the Russian report referred to the initial phase of flight as a “dead period” during which the decrease in physical condition is so severe that none of their countermeasure regimes were sufficiently effective. However, the Russian crewmembers exercise little during the first couple of weeks during flight, which may contribute to the increased HR response noted early during flight.

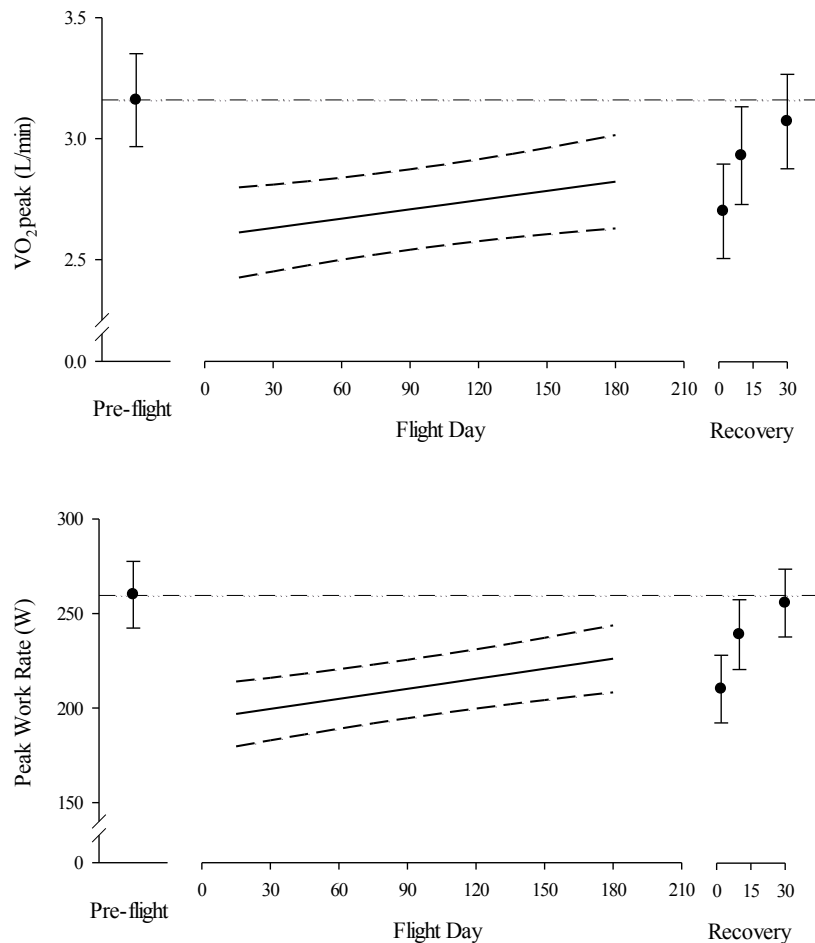
**Maximal Test Results.** Moore et al. measured  $\text{VO}_{2\text{peak}}$  in long-duration ISS astronauts (9 males, 5 females) ~90 days before flight, 15 days after launch (FD15), every ~30 days in-flight, and 1, 10, and 30 days after landing (R+1, R+10, and R+30). The mission durations ranged from 91 to 192 days and occurred during Expeditions 19-33. The peak cycle test protocol consisted of the first 3 stages of the submaximal protocol (3, 5-min stages set at 25%, 50%, and 75% of pre-flight  $\text{VO}_{2\text{peak}}$ ) followed by one-minute stages of 25-Watt increments to volitional fatigue. All tests were performed pre-flight and post-flight in the upright posture on an electronically braked cycle ergometer. All in-flight tests were performed using the CEVIS. Metabolic gas analysis measurements were made to determine  $\text{VO}_{2\text{peak}}$  using the PPFS. Technical details on the PPFS system can be found in the study by Clemensen et al. (Clemensen, Christensen et al. 1994). The main findings of this study were that  $\text{VO}_{2\text{peak}}$  decreased by 17% and peak workload decreased by 24% from pre-flight to ~FD14.  $\text{VO}_{2\text{peak}}$  and peak workload then gradually increased during flight but never returned to pre-flight levels (Figure 14).  $\text{VO}_{2\text{peak}}$  was lower on R+1 (~15%) and R+10 than pre-flight values but recovered by R+30. Peak HR was not different from pre-flight



levels at any time during or following flight. The individual data showed that most, but not all, astronauts with higher initial fitness levels experienced greater decreases from pre-flight to the first in-flight  $\text{VO}_2\text{peak}$  test; however, they typically remained at higher levels than the less fit astronauts. The relationship between initial  $\text{VO}_2\text{peak}$  and the decrease in  $\text{VO}_2\text{peak}$  measured at the first in-flight test was significant ( $R^2 = 0.59$ ;  $P = 0.006$ ) (Moore, Downs et al. 2014).

For the ISS astronauts studied here, the early in-flight decline of  $\text{VO}_2\text{peak}$  is likely due to several factors, including time without exercise in the several days, up to a week, following docking with the ISS, space motion sickness, and cephalic fluid shifts, which contribute to a decrease in blood volume, primarily the plasma component, potentially resulting in decreased muscle perfusion pressure as well as initiating some degree of central cardiovascular deconditioning (Williams, Kuipers et al. 2009). The trend toward improved  $\text{VO}_2\text{peak}$  observed during flight may be due to physiological normalization to the spaceflight environment, as well as the cardiac, blood volume, and peripheral muscle training adaptations expected in individuals who perform regular aerobic exercise.

The post-flight result showing a significant decrease in  $\text{VO}_2\text{peak}$  (~15%) immediately upon landing with a return to pre-flight levels by R+30 is consistent with previous spaceflight investigations (Levine, Lane et al. 1996, Moore, Lee et al. 2001). However,  $\text{VO}_2\text{peak}$  was still below pre-flight levels on R+10 in the astronauts in this study, indicating that the recovery time is longer after ISS missions compared with short-duration Space Shuttle missions.



**Figure 14.** Effect of long-duration spaceflight on absolute  $\text{VO}_2\text{peak}$  and peak work rate during and following ISS missions. The horizontal broken line is a reference drawn at the preflight mean of  $\text{VO}_2\text{peak}$ . The solid line  $\pm$  dashes during flight are the mixed-modeled linear regression mean responses  $\pm$  95% CI (Moore, Downs et al. 2014).

Although most astronauts experienced a decline in  $\text{VO}_2\text{peak}$  during the mission, 4 of the astronauts with average to above-average fitness levels maintained their  $\text{VO}_2\text{peak}$  within 3% of pre-flight values, providing important evidence that aerobic deconditioning is not an inevitable consequence of long-duration spaceflight. These astronauts exercised on the CEVIS at a higher percentage of peak HR ( $79 \pm 6\%$  vs.  $68 \pm 20\%$ , mean  $\pm$  SD) and spent a greater percentage of their time exercising above 70% of peak HR ( $76 \pm 30\%$  vs.  $63 \pm 32\%$ , mean  $\pm$  SD) compared with those who experienced a decrease in  $\text{VO}_2\text{peak}$  (Moore, Downs et al. 2014). These are the first data to show that high-intensity exercise is required for astronauts to maintain  $\text{VO}_2\text{peak}$  during spaceflight. A larger data set is required before recommendations can be made regarding redefining exercise prescriptions and minimal intensity requirements. A current on-going in-flight exercise prescription study (SPRINT) will provide more insight toward exercise prescription recommendations to maintain  $\text{VO}_2\text{peak}$ .

## **1. Effect of Reduced VO<sub>2</sub>peak on Spaceflight Operations**

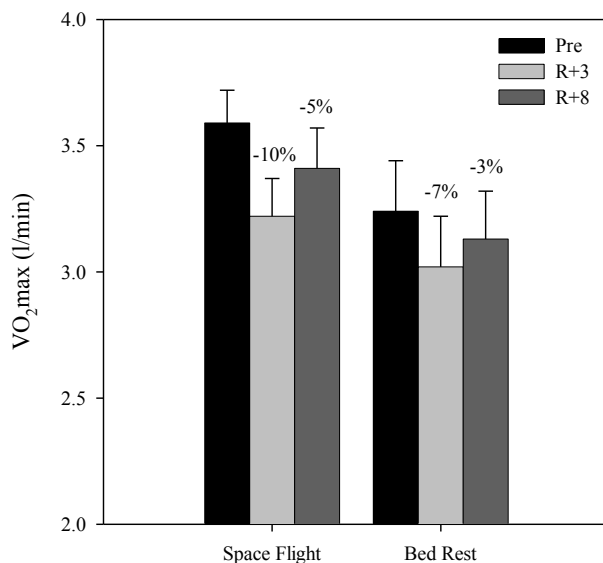
The goal of any countermeasure to spaceflight exposure is to preserve the capability of the crewmembers to perform daily tasks and EVA or emergency egress tasks that may require high levels of work for extended periods of time or in repeated bouts. With regard to routine tasks conducted on board the ISS, the preservation of VO<sub>2</sub>peak is not likely important, as there are few, if any, physically strenuous routine tasks that are performed. ISS EVAs typically elicit an average metabolic cost of  $\sim 200 \text{ kcal}\cdot\text{hr}^{-1}$  ( $\sim 0.7 \text{ Liters O}_2 \cdot \text{min}^{-1}$ ) and have ranged up to  $500 \text{ kcal}\cdot\text{hr}^{-1}$  ( $\sim 1.7 \text{ liters O}_2 \cdot \text{min}^{-1}$ ) (Fortney et al. 1996), which equates to only approximately 50% of the typical VO<sub>2</sub>peak in astronauts. However, EVAs can become aerobically challenging because activity can last for up to 8 hours and it is predominantly upper body in nature (VO<sub>2</sub>peak measured during upper body exercise is approximately 70% of that measured during lower body exercise). The metabolic cost of performing an emergency egress task in the NASA Launch and Entry suit has been reported as ranging from 2.0-2.7 liters O<sub>2</sub>  $\cdot \text{min}^{-1}$ , depending on the amount of G-suit pressurization employed (Bishop, Lee et al. 1999). With regard to EVA on the lunar surface during the Apollo era, several EVAs reportedly were slowed by request of the monitoring flight surgeons because HRs during the activities reached 150-160 beats $\cdot\text{min}^{-1}$  (Portree and Trevino 1997). Until the mission scenarios are defined for future EVA work, it is difficult to predict precisely what VO<sub>2</sub>peak will be required to successfully complete all tasks. However, it is likely that future exploration tasks will be more demanding and will need to be performed with more autonomy, as real-time communication with the ground may not be possible. Consequently, the importance of maintaining VO<sub>2</sub>peak will not diminish as space exploration moves from the ISS to planetary exploration.

## **2. Flight Data Summary**

Aerobic fitness has been evaluated during and following spaceflight starting as early as the Gemini Project. Historically, most data evaluating changes in aerobic fitness during short- and long-duration spaceflight are based on the HR response to submaximal exercise. To date, only two studies have measured VO<sub>2</sub>peak during flight using metabolic gas analysis systems. Levine et al. showed that VO<sub>2</sub>peak is unchanged during short-duration spaceflight (Levine, Lane et al. 1996), and in long-duration ISS astronauts, Moore et al. showed that VO<sub>2</sub>peak is severely impaired early in-flight (i.e., the first 2 weeks) and gradually trends upward during flight but does not reach pre-flight levels (Moore, Downs et al. 2014). Three studies have measured VO<sub>2</sub>peak upon landing (2 conducted on short-duration Space Shuttle astronauts and one on long-duration ISS astronauts) and consistently demonstrate that VO<sub>2</sub>peak is significantly lower on landing day than it is before flight (Levine, Lane et al. 1996, Moore, Lee et al. 2001, Moore, Downs et al. 2014). VO<sub>2</sub>peak appears to recover within 6-9 days following landing after short-duration missions (Levine, Lane et al. 1996, Moore, Lee et al. 2001) but requires a longer time to recover after long-duration missions (Moore, Downs et al. 2014).

## B. Ground-based Spaceflight Analog (Bed Rest)

Human physiology studies during spaceflight are difficult to perform due to the limited number of subjects available and multiple confounding factors, including variable adherence to prescribed countermeasures, inconsistent dietary practices, participation in other science experiments, and interference of specific mission task requirements (Smith, Davis-Street et al. 1997, Trappe, Trappe et al. 2006). Bed rest has become an accepted and established model with which to study changes in physiological function associated with spaceflight, including changes in  $\text{VO}_{2\text{peak}}$ , in a more controlled environment (Fortney, Schneider et al. 1996, Pavy-Le Traon, Heer et al. 2007). In general, the reduction in  $\text{VO}_{2\text{peak}}$  as a result of bed rest is considered to result from the combined effects of reduced physical activity and removal of orthostatic stress (Convertino, Hung et al. 1982). In a direct comparison between responses after spaceflight and bed rest, Trappe et al. (Trappe, Trappe et al. 2006) reported that the decrease in estimated  $\text{VO}_{2\text{peak}}$  during supine cycle ergometry in 4 crewmembers 4 days after a 17-day mission (-10.4%) was comparable to that observed in 8 subjects (-6.6%) 3 days after a 6° head-down tilt bed rest of the same duration (Figure 15).



**Figure 15.**  $\text{VO}_{2\text{peak}}$  before, 3 days after (R+3), and 8 days after (R+8) 17 days in space or bed rest (Trappe, Trappe et al. 2006).

### 1. Changes in $\text{VO}_{2\text{peak}}$ with Bed Rest

Several factors can affect the magnitude of change in  $\text{VO}_{2\text{peak}}$  during bed rest, including the bed rest duration, pre-bed rest fitness level, gender, and whether a countermeasure is performed. The effectiveness of specific exercise countermeasures will be reviewed in greater detail in a later section.

#### a. Duration

In general, there is a rapid decline in  $\text{VO}_{2\text{peak}}$  within the first few days of bed rest and a more gradual loss thereafter (Convertino, Hung et al. 1982). Nixon et al. reported a decrease in estimated  $\text{VO}_{2\text{peak}}$  tested during upright cycle ergometry of 22% (Pre:  $36.4 \pm 2.4$ ; Post:  $28.5 \pm 2.0$ ).

ml·kg<sup>-1</sup>·min<sup>-1</sup>) following only 24 h of 5° head-down tilt bed rest (Nixon, Murray et al. 1979). During bed rest periods up to 30 days, the average decrease in VO<sub>2peak</sub> occurs at a rate of 0.8-0.9 %·d<sup>-1</sup> (Convertino 1996, Convertino 1997, Convertino 2004). However, if VO<sub>2peak</sub> continued to decrease linearly in this manner, the predicted decrease in VO<sub>2peak</sub> would be 42% by 60 days and 72% by 90 days of bed rest, which overestimates the reduction in VO<sub>2peak</sub> in longer duration bed rest studies and would reach zero (death) within 122 days.

Capelli et al. proposed an alternative model based on measurements during 14, 42, and 90-day bed rest studies. Subjects in their studies experienced a decrease in VO<sub>2peak</sub> of 14% on day 14, 16% on day 42, and 32% on day 90 of bed rest (Capelli, Antonutto et al. 2006). The authors speculated that the initial rapid reduction in VO<sub>2peak</sub> was due to decreased maximal Q<sub>c</sub> and circulating hemoglobin levels, while the later slow progressive component was related to muscle atrophy and impairment in peripheral gas exchange. Similarly, Greenleaf et al. observed the greatest rate of decrease in VO<sub>2peak</sub> in the first week of bed rest (Greenleaf, Bernauer et al. 1989).

Decreased VO<sub>2peak</sub> (Convertino 1996) and delayed oxygen kinetics (Convertino, Goldwater et al. 1984) during the first one to two weeks of bed rest are generally associated with decreased circulating blood volume. More recent research has also shown that only five days of bed rest significantly affects cardiac geometry and function (Caiani, Massabuau et al. 2014). Longer simulated microgravity exposures and structural changes in the myocardium (Perhonen, Franco et al. 2001, Dorfman, Levine et al. 2007, Dorfman, Rosen et al. 2008) and the vasculature (Zhang 2001) may increasingly impair exercise capacity as the duration of bed rest increases. For example, bed rest data suggest that left ventricular impairment occurs due to changes in the distensibility of cardiac tissue (Perhonen, Franco et al. 2001, Dorfman, Levine et al. 2007, Dorfman, Rosen et al. 2008) and a reduction in cardiac diastolic function (Levine, Zuckerman et al. 1997). However, the addition of an exercise countermeasure prevented cardiovascular deconditioning after 5 weeks of bed rest (Shibata, Perhonen et al. 2010, Hastings, Krainski et al. 2012). Additionally, negative metabolic adaptations to simulated microgravity, such as reduced citrate synthase activity in skeletal muscle, become apparent after 4 weeks of unloading (Hikida, Gollnick et al. 1989, Berg, Dudley et al. 1993). Longer durations of bed rest are associated with decreased muscle mass, strength, and endurance, which would be expected to impair aerobic exercise performance and decrease the efficacy of the muscle pump to protect venous return (Yang, Baker et al. 2007).

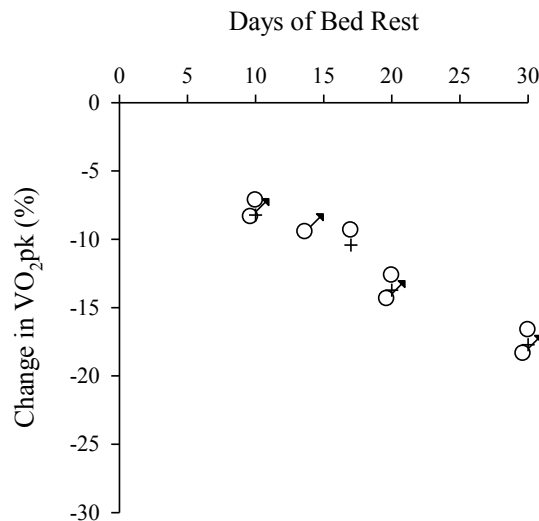
## **b. Pre-Bed Rest Fitness**

Individuals with higher fitness levels have a greater potential for reduction in VO<sub>2peak</sub>. Taylor et al. (Taylor, Henschel et al. 1949) and Saltin et al. (Saltin, Blomqvist et al. 1968) were the first to report that men with a higher VO<sub>2peak</sub> had a greater absolute reduction after bed rest than those with a lower fitness level. Subsequent studies confirmed this finding (Convertino, Stremel et al. 1977, Convertino, Goldwater et al. 1986). Greenleaf and Kozlowski observed that this relationship was strongest when subjects performed peak cycle ergometer tests in the supine position, and the relationship was not strong during upright treadmill testing (Greenleaf and Kozlowski 1982). Conversely, data from the 30-day WISE twin bed rest studies revealed a significant correlation between pre-bed rest fitness and loss in VO<sub>2peak</sub> measured during upright treadmill exercise in both male and female non-exercising subjects (Lee, Schneider et al. 2005, Lee, Schneider et al. 2009). With respect to gender, Convertino et al. (1982) reported that there

was a significant relationship between initial  $\text{VO}_{2\text{peak}}$  and  $\text{VO}_{2\text{peak}}$  measured after 10 days of bed rest in middle-aged and young men ( $r=-0.84$  and  $r=-0.78$ , respectively), but not in either middle-aged or young women ( $r=-0.25$  and  $r=-0.38$ , respectively). The gender difference may be a consequence of the lower pre-bed rest  $\text{VO}_{2\text{peak}}$  values and the shorter bed rest duration. Overall, the data support the contention that those who have higher initial fitness levels are more prone to losses in  $\text{VO}_{2\text{peak}}$  but maintained a higher absolute fitness level compared with their less fit counterparts.

### c. Gender

Few studies have examined the effect of gender on the change in aerobic capacity after bed rest. The studies that have been conducted consistently reported that male subjects had higher pre-bed rest  $\text{VO}_{2\text{peak}}$  values than their female counterparts, and while the percent loss of  $\text{VO}_{2\text{peak}}$  was independent of gender in bed rest durations up to 30 days (Figure 16) (29, 38, 41, 77, 92, 97), the absolute decrease in  $\text{VO}_{2\text{peak}}$  is generally higher in male compared with female subjects (Convertino, Stremel et al. 1977, Convertino, Goldwater et al. 1986, Kashihara, Haruna et al. 1994, Lee, Schneider et al. 2005, Lee, Schneider et al. 2009).



**Figure 16.** The percent change in aerobic capacity ( $\text{VO}_{2\text{peak}}$ ) after bed rest is not different between men and women (Lee, Schneider et al. 2005).

## 2. Mechanisms of Decreased Aerobic Capacity

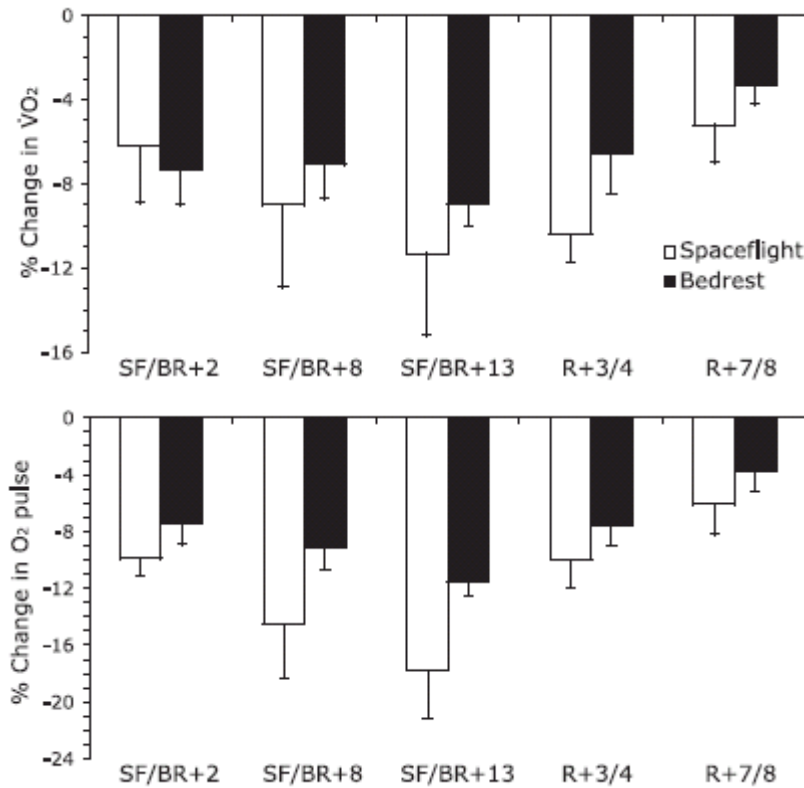
The cardiovascular and peripheral muscle adaptations to bed rest are the primary determinants of changes in  $\text{VO}_{2\text{peak}}$ . From a cardiovascular perspective, changes in cardiac output ( $Q_c$ ), venous return, and plasma volume are important effectors of  $\text{VO}_{2\text{peak}}$ . Potential deficits in arteriovenous oxygen difference, red blood cell mass, perfusion, orthostatic tolerance, and thermoregulation are also important factors to consider in understanding bed rest-induced changes in  $\text{VO}_{2\text{peak}}$ .

**a. Cardiac Output ( $Q_c$ )**

Cardiac output ( $Q_c$ ) is the product of heart rate (HR) and stroke volume (SV). In ambulatory subjects, it has been postulated that the primary determinant of  $VO_{2peak}$  is maximal  $Q_c$ . Although the debate continues in scientific journals, many have argued that the capacity of the muscular system to increase vascular conductance and oxygen consumption is greater than the ability of the human heart to pump blood (Andersen and Saltin 1985, Saltin 1985, Rowell 1986, Noakes 2005, Saltin, Calbet et al. 2006). Supporting the view that maximal  $Q_c$  is a primary limiting factor after bed rest, the reduction in  $Q_c$  in 5 male subjects following 21 days of bed rest (-26%) was similar to the reduction in  $VO_{2peak}$  (-26%) (Saltin, Blomqvist et al. 1968). Similarly, using radionuclide imaging in 12 middle-aged men, Hung et al. observed a 23% decrease in maximal  $Q_c$  and a 17% decrease in  $VO_{2peak}$  following 10 days of bed rest (Hung, Goldwater et al. 1983). However, this relationship between the decrease in maximal  $Q_c$  and lower  $VO_{2peak}$  after bed rest does not appear to remain as the duration of bed rest is extended. Capelli et al. reported that the decrease in  $Q_c$  after 42 and 90 days of bed rest was not significantly different than that measured after 14 days of bed rest, suggesting that peripheral factors at the level of the working muscle were responsible for further decrements in  $VO_{2peak}$  (Capelli, Antonutto et al. 2006). In contrast, Ferretti et al. reported that maximal  $Q_c$  was reduced to a greater extent than  $VO_{2peak}$  (-31% and -17%, respectively) after 42 days of bed rest (Ferretti, Antonutto et al. 1997). A non-traditional peak cycle protocol was used in this study; each incremental stage was 5 minutes in duration but separated by a 5-minute rest period. It is possible that this protocol did reflect the true change in  $VO_{2peak}$ .

In general, maximal HR has been observed to be unchanged or increase slightly after short- and long-duration periods of bed rest (Convertino 1996, Fortney, Schneider et al. 1996, Capelli, Antonutto et al. 2006); therefore, it is not likely a contributing factor to lower maximal  $Q_c$  values. Maximal HR was unchanged following 24 h of bed rest (Nixon, Murray et al. 1979), but in a separate study, it was observed to increase during both supine (5.7%) and upright (5.9%) cycle exercise following a 10-day bed rest (Convertino, Hung et al. 1982). The effects of exercise countermeasures on maximal HR after bed rest are inconsistent. Recently, maximal HR was unchanged in control subjects following 30 days of bed rest and was decreased when an exercise countermeasure was employed (Lee, Schneider et al. 2005); however, it was increased after bed rest with and without an exercise countermeasure in another study (Stremel, Convertino et al. 1976).

Reduced SV is the primary contributor to the decrease in maximal  $Q_c$ . Hung et al. reported that after 10 days of bed rest, the reduction in  $Q_c$  was solely the result of a 28% reduction in exercise SV (Hung, Goldwater et al. 1983). Similarly, maximal oxygen pulse, considered to be an index of SV, was reduced after 10 (Convertino 1987) and 17 days (Trappe, Trappe et al. 2006) of bed rest during supine ergometry, and comparable responses were noted in four astronauts following a spaceflight of the same duration (Figure 17) (Trappe, Trappe et al. 2006). Ferretti et al. reported that the 31% decrease in maximal  $Q_c$  following 42 days of bed rest was due solely to a 31% reduction in maximal SV because maximal HR was unchanged (Ferretti, Antonutto et al. 1997). Resting and submaximal exercise SV were also reduced during long-duration bed rest (Ferretti, Girardis et al. 1998, Sundblad, Spaak et al. 2000, Spaak, Montmerle et al. 2005) and spaceflight (Atkov, Bednenko et al. 1987).



**Figure 17.** Oxygen consumption ( $\dot{V}O_2$ ) and  $O_2$  pulse changes during exercise during and after both spaceflight and bed rest. Spaceflight data were collected at 85% of the preflight maximal workload, while bed rest data were collected at maximal effort (Trappe, Trappe et al. 2006).

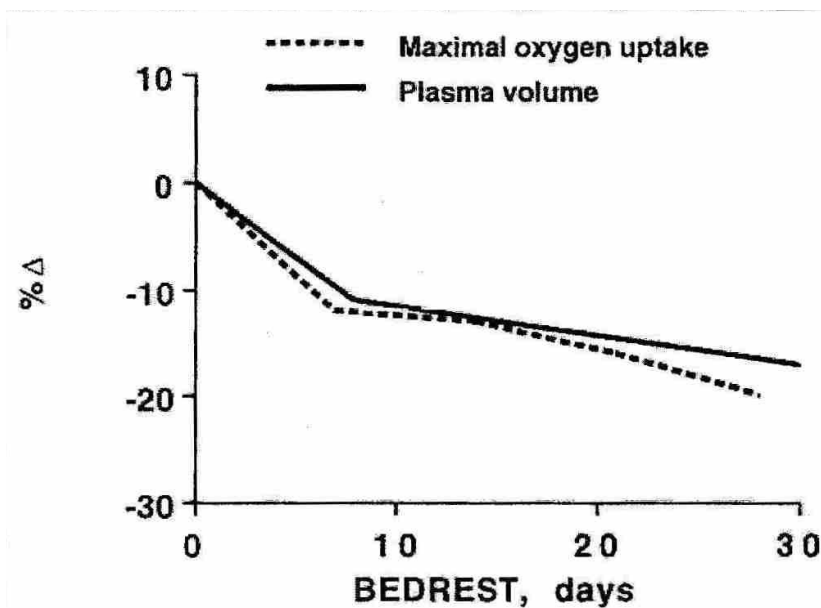
Although exercise SV is consistently reduced with bed rest, studies reporting the effects of bed rest on cardiac function are not consistent. Convertino et al. showed an increase in ejection fraction and suggested that ventricular performance is maintained while venous return and cardiac filling may be impaired (Convertino 1997). In contrast, more recent bed rest data suggest that left ventricular impairment occurs due to changes in the distensibility of cardiac tissue (Perhonen, Franco et al. 2001, Dorfman, Levine et al. 2007, Dorfman, Rosen et al. 2008) and a reduction in cardiac diastolic function (Levine, Zuckerman et al. 1997). Cardiac atrophy, measured using magnetic resonance imaging, appears to occur by 14 days of bed rest, which likely contributes to reduced cardiac distensibility and smaller SV for a given filling pressure. Left ventricular mass decreased in men by 5, 8, and 16% after 2, 6, and 12 weeks of bed rest, respectively (Perhonen, Franco et al. 2001). Additionally, left ventricular end-diastolic volume decreased by 14% after 2 weeks of bed rest but changed only minimally thereafter. Similar observations were made in women after 60 days of bed rest (Dorfman, Levine et al. 2007). There is evidence that the addition of an exercise countermeasure during bed rest prevents or mitigates losses in cardiac function (Shibata, Perhonen et al. 2010, Hastings, Krainski et al. 2012).

#### b. Plasma Volume

Previous investigations have consistently demonstrated that plasma volume is rapidly reduced during exposure to spaceflight and bed rest, with the majority of the initial loss



occurring within 1-2 days (Blomqvist 1983). Plasma volume has been observed to be decreased in as little as 6 h, reaching a 10% loss in 24 h and equaling approximately 12% by the third day of bed rest (Nixon, Murray et al. 1979). Greenleaf et al. have suggested that the loss of plasma volume is progressive through 60 to 80 days of bed rest (Greenleaf, Bernauer et al. 1977). The time course of the decrease in plasma volume is similar to that of the decrease in exercise capacity (Figure 18), and the mean loss of plasma volume across studies has been reported to account for approximately 70% of the variability in the mean decrease in  $\text{VO}_{2\text{peak}}$  following up to 30 days of bed rest (Convertino 1997). Reduced circulating plasma volume may negatively affect exercise SV, the delivery of oxygen and nutrients to working muscle, and the removal of metabolic waste products. Thus, preservation of plasma volume has been suggested to be an important factor in the maintenance of exercise capacity during bed rest and may be even more important during upright than supine exercise because of the addition of gravitational stress.



**Figure 18.** Decreased maximal oxygen consumption in subjects who perform no countermeasures appears to parallel losses of plasma volume up to 30 days of bed rest (Convertino 1997).

Maintenance of plasma volume alone is likely not the only determinant of exercise capacity preservation, especially following longer duration bed rest studies. Blomqvist et al. (17) provided sufficient amounts of saline through infusion to restore the central venous pressure to the pre-bed rest levels following a 24-h bed rest. Although this procedure was not protective of orthostatic tolerance, it did abolish the loss of upright  $\text{VO}_{2\text{peak}}$  (Blomqvist, Nixon et al. 1980). However, Stremel et al. maintained plasma volume (-8%, NS) in subjects during 14 days of bed rest by employing two daily 30-minute bouts of supine cycle exercise at 68% of pre-bed rest  $\text{VO}_{2\text{peak}}$ , but supine  $\text{VO}_{2\text{peak}}$  (-9%) and submaximal exercise responses were not maintained. In addition, subjects who performed an isometric exercise regimen during the same study experienced loss of plasma volume that was similar to that in the non-exercise control subjects (-15% vs. -10%), but the decrease in  $\text{VO}_{2\text{peak}}$  was not as great (-5%) in the isometric exercise group (Stremel, Convertino et al. 1976). In a separate study, restoration of plasma volume at the end of a 16-day bed rest following an intense exercise bout did not successfully maintain  $\text{VO}_{2\text{peak}}$  (Engelke and Convertino 1998).

When reporting the results of plasma volume and  $\text{VO}_2\text{peak}$  for individual subjects, the relationship between these two outcomes may not be as strong as that when comparing mean results for a group of subjects. In general, there appears to be more variability in the plasma volume response to bed rest than in the decrease in  $\text{VO}_2\text{peak}$ . Additionally, as the duration of the bed rest period increases, the strength of the relationship appears to decrease. Following 14 days of bed rest, in control subjects and subjects participating in a countermeasure employing a reverse pressure gradient garment, the decrease in  $\text{VO}_2\text{peak}$  was significantly related to the loss of plasma volume ( $r^2=0.56$ ) (Convertino, Sandler et al. 1982). Recently, in a study of male control and exercise countermeasure subjects, the change in plasma volume from pre-bed rest accounted for only 24% of the variance in upright  $\text{VO}_2\text{peak}$  after 30 days of bed rest (Lee, Schneider et al. 2009). In a companion study utilizing female control and exercise subjects, there was no significant change in plasma volume in either the control or countermeasure subjects, although only the control subjects experienced a significant loss of  $\text{VO}_2\text{peak}$ . The lack of change in plasma volume in both the female control and exercise subjects appears to support a previous observation that  $\text{VO}_2\text{peak}$  is not strongly related to the change in plasma volume with bed rest (Lee, Schneider et al. 2009).

### **c. Orthostatic Stress**

The influence of gravity on work performance is apparent when comparing results from supine versus upright exercise capacity after equal durations of simulated microgravity. After short-duration bed rest,  $\text{VO}_2\text{peak}$  decreased 2-2.5 times more during upright exercise compared with supine exercise (Convertino, Hung et al. 1982, Convertino, Goldwater et al. 1982). After 10 days of bed rest in middle-aged men, the reduction in  $\text{VO}_2\text{peak}$  was 15% in the upright posture but was only 6% (N.S.) when subjects were tested in the supine posture (Convertino, Hung et al. 1982). Submaximal exercise responses are similarly affected; at 115 Watts, HR was elevated by 4% above pre-bed rest values when subjects performed supine ergometry but was increased by 8% when the exercise was performed upright. Exercise in the upright posture is associated with a greater reduction in SV and  $Q_c$  than supine exercise. Saltin et al. reported that both resting and exercise SVs were reduced to a greater extent when subjects were upright (Rest: -24%, Exercise: -35%) than when the subjects were supine (Rest: -17%, Exercise: -23%) (Saltin 1985).

Exercise alone prevents the loss of  $\text{VO}_2\text{peak}$  when pre- and post-bed rest tests are performed in the supine posture. A potential relationship between the preservation of orthostatic tolerance and exercise performance by implementation of a single countermeasure would be an attractive feature to NASA. During recent studies utilizing exercise and lower body negative pressure (LBNP) as an orthostatic stressor, the countermeasure subjects maintained  $\text{VO}_2\text{peak}$  (Watenpaugh, Ballard et al. 2000, Lee, Schneider et al. 2009) and experienced smaller bed rest-induced changes in cardiovascular responses during orthostatic stress (Schneider, Watenpaugh et al. 2002) and attenuated orthostatic intolerance (Watenpaugh, O'Leary et al. 2007). The use of these data to specifically link orthostatic tolerance and exercise capacity is hindered when relying upon these data sets alone because the countermeasure is a combination of exercise and orthostatic stress.

#### **d. Venous Return**

Decreased venous return may be the result of an increase in lower body venous compliance and reduced plasma volume that has been commonly observed after bed rest (Convertino 1997). Although multiple vascular factors contribute to limb compliance, changes in muscle mass and tonicity associated with bed rest may contribute to increase venous pooling when the mechanical obstruction to venous stretching and accumulation of blood are reduced. Following 30 days of bed rest, calf compliance was increased (2.4%), concomitant with a decrease in muscle volume (-5%) (Convertino, Doerr et al. 1989). In this bed rest study, changes in muscle cross-sectional area explained approximately 50% of the variability in the change in calf compliance. When subjects are exercising, it is recognized that cardiac filling pressure, SV, and  $Q_c$  are supported by the expulsion of blood from the active muscles by the “muscle pump,” but these mechanisms will be of little importance in non-active muscles and other compliant regions of the circulation.

Blood may pool in other areas of the body after bed rest, including the splanchnic region, which would affect venous return during exercise. Savilov et al. used radioisotope tracers to measure translocation of blood during LBNP, an orthostatic stressor. Subjects with low orthostatic tolerance displayed a marked increase in blood pooling in the abdomen during LBNP, with reflective decreases in blood distribution to the head and chest. Subjects with relatively better LBNP tolerance had less extreme responses (Savilov, Lobachik et al. 1990). Similarly, Fischer et al., (2007) reported that splanchnic blood flow was higher at each level of LBNP following just 4 h of bed rest, and this was associated with an increased HR and reduced volumes (Fischer, Arbeille et al. 2007).

The reduction in vasoconstrictive reserve that Convertino and Cooke suggest as a factor in orthostatic intolerance after bed rest and spaceflight may also contribute to reduced exercise capacity (Convertino and Cooke 2002). Following 16 days of bed rest, elevated vasoconstriction was evident at rest in response to reduced plasma and SVs (Engelke, Doerr et al. 1996), and maximal vascular resistance was unchanged but was achieved at a lower level of orthostatic stress induced by a graded LBNP protocol (Convertino 1999). An inability to vasoconstrict – particularly in the venous system, which contains 70% of the total blood volume of a resting subject – impairs the ability to compensate for decreased blood and plasma volume, especially when coupled with orthostatic stress, to maintain venous return and SV during exercise.

Linked to this, changes in the sympathetic nervous system response to exercise may be important to  $VO_{2peak}$  with regard to the appropriate distribution of blood flow. Specifically, there is an inverse relationship between norepinephrine concentrations and splanchnic blood flow. Rowell calculated, for example, that regional vasoconstriction in the splanchnic organs, kidneys, and skin can provide an additional 600 ml of  $O_2$  per minute at maximal exercise in normal ambulatory subjects (Rowell 1986). Elevated levels of circulating norepinephrine may be an important adaptation to reduced blood volume to defend muscle blood flow and restrict flow to the splanchnic region and other inactive tissues (Engelke and Convertino 1996). Sympathetic nervous system activity and catecholamine levels in resting subjects have been reported to be either unchanged or decreased following bed rest, and elevated HR in resting subjects has been ascribed to reduced vagal control (Convertino, Bloomfield et al. 1997). Following 3 days of bed rest, the norepinephrine levels during submaximal exercise tended to be higher and the norepinephrine threshold was lower in endurance athletes following bed rest, but these alterations were not evident in sedentary subjects (Smorawinski, Nazar et al. 2001). There was, however, no difference in maximal norepinephrine concentrations or epinephrine responses in either group. In contrast, following 16 days of bed rest, Engelke and Convertino (Engelke and

Convertino 1996) reported that plasma norepinephrine concentrations were 64% greater at peak exercise although the peak HR was only 5% higher. However, no changes in epinephrine were reported during rest or maximal exercise.

#### **e. Arteriovenous Oxygen Difference**

Maximal systemic oxygen extraction, assumed to be at the level of the working muscle, does not appear to be affected by short-duration bed rest. There was little change in the arteriovenous difference in middle-aged men following 10 days of bed rest (Hung, Goldwater et al. 1983), and it was unchanged after 21 days of bed rest in five male subjects (Saltin, Blomqvist et al. 1968). In general, the maximal extraction of oxygen from the systemic circulation does not appear to be specifically affected by bed rest, but oxygen extraction during submaximal exercise appears to be increased to compensate for the lower hemoglobin concentration during longer durations of bed rest (Ferretti 1997). However, it is not clear from these data whether blood flow is appropriately directed to working muscle and whether the extraction at the level of muscle itself is maintained.

Delivery of oxygen to the muscle has been suggested to be impaired after bed rest. Resting leg blood flow (Blamick, Goldwater et al. 1988) and peak vascular conductance, which has been associated with  $\text{VO}_2$  max in ambulatory subjects (81, 101, 124, 149), are reduced following bed rest (Snell, Martin et al. 1987, Blamick, Goldwater et al. 1988, Convertino, Doerr et al. 1989, Martin, Ogawa et al. 1991, Reading, Goodman et al. 1993, Kosmas, Hussain et al. 1996, Engelke and Convertino 1998). The reduction in vascular conductance was associated with a decreased resistance to fatigue of the calf muscle, but when peak vascular conductance was restored with a maximal bout of exercise at the end of bed rest,  $\text{VO}_{2\text{peak}}$  was not similarly protected (Engelke and Convertino 1998). However, peak vascular conductance was associated with  $\text{VO}_{2\text{peak}}$  before and after bed rest, suggesting that the protection of peripheral mechanisms associated with the oxygen utilization in the muscle is not effective unless central cardiac effects are restored (Engelke and Convertino 1998). Additionally, Hikida et al. reported a 37% decrease in the capillary-to-fiber ratio of the soleus following 30 days of bed rest (Hikida, Gollnick et al. 1989), although Ferretti et al. (51) observed no change in either the capillary density or capillary-fiber ratio in the vastus lateralis (Ferretti 1997).

#### **f. Decreased Red Blood Cell Mass**

Red cell mass has been reported to be decreased in as little as 7 days of bed rest (Convertino, Goldwater et al. 1982), although the most consistent results are observed at bed rest day 14 (Fortney, Schneider et al. 1996), and red cell mass may continue to decline for a short period during the recovery from bed rest (Scianowski, Kedziora et al. 1995, Fortney, Schneider et al. 1996, Lee, Williams et al. 2002). Convertino et al. reported that red cell volume was decreased by 11% during 14 days of bed rest, independent of whether the subject performed countermeasures or participated in a protocol to simulate the effects of orthostatic stress (Convertino, Sandler et al. 1982). Exercise during bed rest may prevent the loss of red cell mass; however, exercise that is too intense has the potential to cause red cell destruction (Fortney, Schneider et al. 1996).

The correlation between the change in red cell mass and the change in  $\text{VO}_{2\text{peak}}$  is low in short- and moderate-duration bed rest studies (Convertino 1997). In general, hematocrit does not change during bed rest, suggesting that the oxygen carrying capacity per unit of blood is unchanged (Convertino, Sandler et al. 1982, Convertino 1997). However, as red cell mass

continues to decline with longer bed rest, albeit at a slower rate, the total oxygen delivery capacity of the blood is reduced at rest and during submaximal exercise and further impaired at maximal exercise when maximal  $Q_c$  is also reduced (Ferretti, Antonutto et al. 1997, Ferretti, Girardis et al. 1998, Pavy-Le Traon, Heer et al. 2007). Capelli et al. reported that hemoglobin concentration was decreased by 9% after 42 days of bed rest, which along with the decrease in  $Q_c$  was reflected by a 34% decrease in total oxygen delivery. However, arterial saturation of hemoglobin was unchanged during bed rest (Ferretti, Antonutto et al. 1997, Capelli, Antonutto et al. 2006).

#### **g. Cerebral Perfusion**

Inadequate cerebral perfusion during post-bed rest exercise may also impair exercise performance, particularly when performed against an orthostatic stress. Prior to 30 days of bed rest, the majority of subjects terminated graded exercise tests due to general fatigue and shortness of breath (92). After bed rest, half of the control subjects who performed no countermeasures reported lightheadedness or loss of balance as the primary reasons for test termination. In contrast, fatigue and shortness of breath remained the predominant symptoms at test termination after bed rest in a group of subjects who performed an exercise countermeasure that maintained  $VO_{2peak}$  (Lee, Schneider et al. 2009).

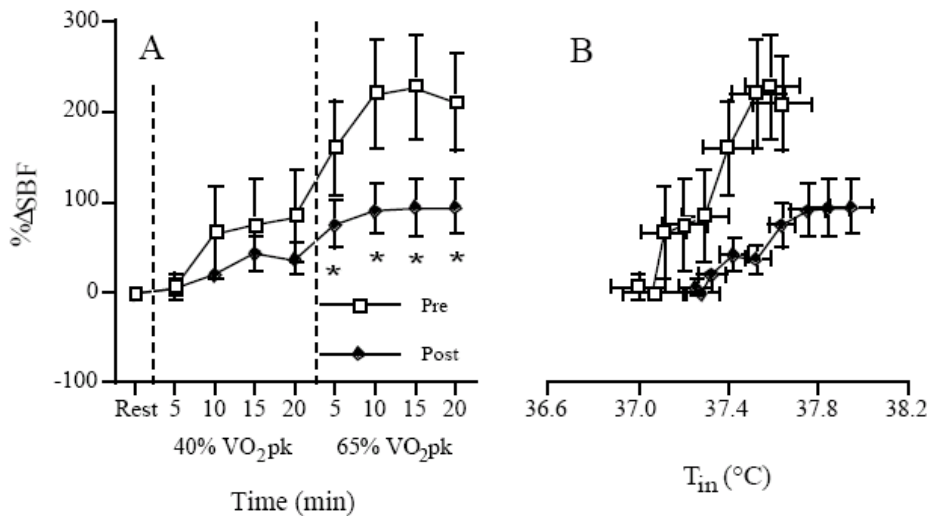
Reduced exercise capacity after bed rest may also be related to changes in central command. The strength of voluntary maximal muscle contraction is reduced to a greater extent (-36%) than muscle tension (-24%), which is electrically evoked. The difference between these two muscle tensions, termed the force deficit, increased by 40% during bed rest (Koryak 1998). If muscle performance is inhibited in this manner following a period of unloading,  $VO_{2peak}$  and  $Q_c$ , according to the “oxygen pull” model, would also consequently be reduced (Noakes 2005). Inadequate cerebral blood flow and local brain ischemia may further exacerbate this.

#### **h. Thermoregulatory Changes**

Physical work capacity after bed rest and spaceflight may be further reduced by impaired body temperature regulation during rest and exercise that, in turn, may lead to heat strain and injury. With regard to spaceflight, the combined effects of plasma volume loss and loss of heat acclimation may result in excessive heat strain for crewmembers wearing protective garments during launch and landing (Pandolf, Stroschein et al. 1995). During a nominal landing (STS-90, April 1998) prior to exit from the Space Shuttle, intestinal temperature (core temperature) was significantly elevated in four crewmembers wearing the required Launch and Entry Suit (LES) despite the use of a liquid cooling garment (Rimmer, Djik et al. 1999). In the event of an emergency egress from the Shuttle, crewmembers would be disconnected from the thermoelectric cooling unit supplying the liquid cooling garment to exit the vehicle, and they would then be required to ambulate to a safe distance. This activity would be completed fully suited and may require an effort in excess of 70% of the crewmember's pre-flight  $VO_{2peak}$  (Bishop, Lee et al. 1999). The combined thermal load of the protective garment and the elevated metabolic rate during egress would likely rapidly increase the core temperature.

Impaired thermoregulation at rest and during exercise is evident after bed rest. Crandall et al. passively heated subjects with a warm water-perfused suit before and after 15 days of bed rest. After bed rest, these subjects had a reduced forearm blood flow and vascular conductance before and during whole body heating (Crandall, Shibasaki et al. 2003). Michikami et al., using similar techniques, also observed an increase in the threshold temperature and decreased

sensitivity of the vascular conductance and sweating response following 14 days of bed rest (Michikami, Kamiya et al. 2004). A higher core temperature has been observed after bed rest during submaximal exercise under both warm and temperate conditions (Greenleaf and Reese 1980, Fortney 1987, Ertl, Dearborn et al. 2000, Smorawinski, Nazar et al. 2001, Lee, Williams et al. 2002). The elevated post-bed rest core temperature during exercise was ascribed to a decreased ability to increase skin blood flow and impaired sweating responses (Greenleaf and Reese 1980, Greenleaf 1997, Lee, Williams et al. 2002) (Figure 19). However, the performance of an exercise countermeasure during bed rest has been shown to prevent these thermoregulatory adaptations and preserve  $\text{VO}_{2\text{peak}}$  (Shibasaki, Wilson et al. 2003).



**Figure 19.** The change in skin blood flow in response to increasing core temperature during submaximal exercise is reduced after bed rest (Panel A). The onset of the vasodilatory response was delayed and the slope of the response tended to be reduced (Panel B) (Lee, Williams et al. 2002).

### 3. Recovery after Bed Rest

The time course of the recovery of  $\text{VO}_{2\text{peak}}$  following bed rest is dependent on the bed rest duration and the degree of deconditioning. Some improvement in exercise responses is apparent within a few days of reambulation. Similar to the data reported for spaceflight, this is largely associated with a recovery of plasma volume, which is particularly apparent during submaximal exercise. For example, the HR response to treadmill walking was significantly elevated on the first day of reambulation following a recent 60-day bed rest study but was not different than pre-bed rest 2 days later, even though  $\text{VO}_{2\text{peak}}$  was still significantly lower (-21%) than the pre-bed rest value (Schneider, Lee et al. 2009). Similarly, there was some recovery of submaximal HR during supine ergometry (150 W) 3 days after a 17-day bed rest period compared with the last in-bed rest test, even though  $\text{VO}_{2\text{peak}}$  was still depressed compared with pre-bed rest values (-7%) (Trappe, Trappe et al. 2006). Although the time course for recovery of post-bed rest plasma volume has not been well characterized, preliminary data from 90-day bed rest studies suggest that plasma volume on average is restored after 3 to 4 days of ambulatory recovery in non-exercise control subjects (Dr. Steven Platts, personal communication).

Recovery of  $\text{VO}_2\text{peak}$  normally occurs within 2 to 4 weeks after bed rest lasting 30 days or longer (DeBusk, Convertino et al. 1983). Recovery is much faster after a shorter duration of bed rest. For example,  $\text{VO}_2\text{peak}$  was 6.6% below pre-bed rest levels after only 3 days of reambulation and was ~3% below pre-bed rest levels after 1 week of reambulation. A similar amount of recovery (50%) was observed in four crewmembers after a spaceflight of the same duration (R+8: -5.2%, R+3: -10.4%) (Trappe, Trappe et al. 2006). Saltin et al. reported that the aerobic capacity of 3 of 5 bed rest subjects who participated in 21 days of bed rest was restored within 10 to 14 days after resuming normal activities. Additionally, more fit subjects appear to return to their pre-bed rest fitness levels more slowly than their less fit counterparts, although the previously more highly fit subjects are likely to perform better at all time points than if they had been previously unfit (Saltin, Blomqvist et al. 1968).

Following 60- and 90-day bed rest studies conducted by the NASA Johnson Space Center,  $\text{VO}_2\text{peak}$  estimated from submaximal exercise tests was improved during the recovery period (from R+2 to R+11) in most subjects, but it remained 10% lower than pre-bed rest  $\text{VO}_2\text{peak}$  values in 5 of the 9 subjects (Dr. Don Hagan, unpublished observations). All of the bed rest subjects participated in a daily 1-h program of supervised ambulation and exercise during the post-bed rest period. The program consisted of 10-15 minutes of walking as well as calisthenics to strengthen the muscles of the trunk, upper body, and legs. The primary objective of the reconditioning plan was to restore the functional mobility and capacity to perform activities of daily living in preparation for release from bed rest. Since the protocol was not targeted specifically at increasing  $\text{VO}_2\text{peak}$ , it is not surprising that recovery of  $\text{VO}_2\text{peak}$  was incomplete. Similarly, Sundblad et al. and Spaak et al. observed that submaximal heart rate was elevated 12 and 15 days, respectively, after 42 days of bed rest but returned to pre-bed rest levels when tested 32 days after bed rest (Sundblad, Spaak et al. 2000, Spaak, Montmerle et al. 2005).

#### **4. Submaximal Exercise Responses**

Changes in  $\text{VO}_2\text{peak}$ , HR response to submaximal exercise, and lactate threshold may occur independently of changes in  $\text{VO}_2\text{max}$  (Caiozzo, Davis et al. 1982), which could signal a potential for earlier onset of fatigue and impaired ability to perform sustained tasks. Aerobic deconditioning after bed rest is evident by higher HR, ventilation, respiratory exchange ratio, and rating of perceived exertion during submaximal exercise (Nixon, Murray et al. 1979, Convertino, Goldwater et al. 1982, Convertino, Sandler et al. 1982, Convertino 1996, Convertino 1996, Fortney, Schneider et al. 1996, Lee, Bennett et al. 1997, Watenpaugh, Ballard et al. 2000, Smorawinski, Nazar et al. 2001, Katayama, Sato et al. 2004a, Lee, Schneider et al. 2009). Of these, elevated HR during submaximal exercise is the most prominent feature of bed rest-induced deconditioning. Submaximal exercise HR was increased following 24 h of bed rest by approximately  $20 \text{ beats} \cdot \text{min}^{-1}$ , which Nixon et al. noted was similar to the increase observed in Apollo and Skylab astronauts following spaceflight (Nixon, Murray et al. 1979). During 17 days of bed rest, submaximal HR at 150 Watts was significantly increased by the eighth day of bed rest and remained elevated throughout the first post-bed rest exercise test (Trappe, Trappe et al. 2006). Bed rest studies that incorporate an aerobic exercise countermeasure show mixed results, where the effectiveness of the countermeasure appears to be related to the prescribed exercise intensity. Submaximal exercise HR was increased at almost every stage during supine ergometry following 14 days of bed rest, regardless of whether subjects performed a moderate intensity exercise countermeasure (Stremel, Convertino et al. 1976). However, when subjects performed a countermeasure that preserves  $\text{VO}_2\text{peak}$ , submaximal HR was unchanged compared with pre-bed

rest levels (Watenpaugh, Ballard et al. 2000, Katayama, Sato et al. 2004a, Lee, Schneider et al. 2005, Lee, Schneider et al. 2009).

Elevated submaximal exercise HR after bed rest is likely a compensatory mechanism to maintain  $Q_c$  when SV is decreased. Following 20 days of bed rest, submaximal  $Q_c$  was not different during upright exercise, although HR was increased and SV was reduced in subjects performing no countermeasures (Katayama, Sato et al. 2004b). A 3-day bed rest study investigated the cardiovascular responses at rest and during submaximal exercise in sedentary and endurance-trained subjects after 3 days of bed rest. At rest, HR increased and SV was reduced in both sedentary and endurance-trained subjects, whereas SV was reduced and HR was elevated only in the sedentary subjects during submaximal exercise. The fact that no change was observed in endurance athletes may have been because the submaximal workloads (up to 150 W) represented a proportionally lower percentage of their maximal exercise capacity (Peak Watts: Control = 188, Endurance = 270)) (Smorawinski, Nazar et al. 2001). Other changes in the submaximal exercise response associated with detraining include elevated ventilation and respiratory exchange ratio (Mujika and Padilla 2000).

Lactate threshold may be the most important predictor of exercise performance and the ability to perform sustained tasks, as may be required during EVAs or future exploration missions. To date, only one study has measured the effects of bed rest on lactate threshold and showed that the decrease in lactate threshold was far greater than the decrease in  $VO_{2peak}$  (25% vs. 7%) following 10 days of bed rest (Convertino, Karst et al. 1986). Others have measured blood lactate during submaximal exercise and shown higher concentrations post-bed rest compared with pre-bed rest (Saltin, Blomqvist et al. 1968, Sullivan, Binkley et al. 1985, Convertino, Karst et al. 1986, Williams and Convertino 1988, Smorawinski, Nazar et al. 2001). The effect of bed rest on the lactate threshold may be more apparent in more highly trained subjects, who also experience a decrease in the norepinephrine response threshold during graded exercise after 3 days of bed rest (Smorawinski, Nazar et al. 2001). The impaired ability of skeletal muscle to utilize aerobic pathways after bed rest for energy utilization may be inferred from the loss of aerobic pathway enzymes (Hikida, Gollnick et al. 1989) and reduced glucose transporter content (Tabata, Suzuki et al. 1999) or to a reduced or an inappropriate distribution of blood flow, as has been observed in animal models during exercise (Woodman, Sebastian et al. 1995).

## **5. Countermeasures**

The optimal countermeasure prescription for the prevention of spaceflight-induced deconditioning should ideally include components to stimulate or maintain each organ system's condition similar to that maintained in a normal gravity environment, and it should require a minimal amount of crewmember time (Vernikos, Ludwig et al. 1996). The total time currently allowed for resistive and aerobic exercise on the ISS, including set-up and stowage of the exercise hardware and personal hygiene, is only 2.5 h per day. Countermeasures that are too long or too intensive may reduce compliance in some crewmembers and may be difficult for schedulers to accommodate among various mission-critical tasks. It is paramount that the countermeasures employed to protect crew health be of sufficient efficacy to promote and maintain high levels of function, such as aerobic and anaerobic fitness, in both male and female astronauts. Care must be taken, however, when attempting to implement countermeasures that



were successful in bed rest in the spaceflight environment due to logistical constraints of the spaceflight environment. In addition to crew time, exercise hardware mass, volume, and stowage should be considered as well as the impacts of countermeasure performance on the environmental control systems.

Although the preservation of  $\text{VO}_2\text{peak}$  and exercise performance after short-duration bed rest studies primarily may be achieved through protecting against blood volume losses and changes in SV, the maintenance of  $\text{VO}_2\text{peak}$  during longer bed rest exposures also likely requires the maintenance of aerobic pathway enzymes (72), muscle strength and endurance, neuromuscular coordination, muscle capillary density, and cardiac mass and function (Hikida, Gollnick et al. 1989, Perhonen, Franco et al. 2001, Dorfman, Levine et al. 2007).

#### **a. Exercise**

Exercise is a natural modality to consider when developing countermeasures to the decrease in  $\text{VO}_2\text{peak}$  during and after bed rest. Longer duration bed rest studies (>30 days) that employ an exercise countermeasure show mixed results with respect to the ability to protect  $\text{VO}_2\text{peak}$ . In general, it appears that moderate to high intensity daily exercise is required to provide some level of protection of  $\text{VO}_2\text{peak}$ . While there are no ISS flight studies that have specifically investigated the effect of in-flight exercise frequency, time, or intensity on the preservation of  $\text{VO}_2\text{peak}$ , Moore et al. showed that  $\text{VO}_2\text{peak}$  was better preserved in the astronauts who performed in-flight exercise at higher intensities compared with those who engaged in lower intensity exercise (Moore, Downs et al. 2014). There are currently sister studies, one in-flight ISS study and one 70-day bed rest study, that focus on low-volume, high-intensity aerobic and resistance exercise and their effectiveness in maintaining muscle, bone, and cardiovascular health. Upon completion, these studies will provide valuable information with respect to exercise dose requirements to maintain cardiovascular fitness in bed rest and during ISS missions.

From the existing bed rest studies, it is clear that moderate intensities of aerobic exercise are not consistently effective to prevent the loss of  $\text{VO}_2\text{peak}$ . For example, Stremel et al. were unable to prevent the decrease in  $\text{VO}_2\text{peak}$  and plasma volume during two weeks of bed rest when subjects performed two daily 30-minute bouts of supine cycle ergometry at an intensity of 68% of pre-bed rest  $\text{VO}_2\text{peak}$  (Stremel, Convertino et al. 1976). However, Shibasaki et al. maintained  $\text{VO}_2\text{peak}$  and plasma volume during 14 days of bed rest with 90 minutes of daily exercise at 75% pre-bed rest HR (Shibasaki, Wilson et al. 2003). Short, intense bouts of exercise in ambulatory subjects are considered to be more effective than longer, less strenuous exercise in promoting changes in aerobic fitness in ambulatory subjects (Wenger and Bell 1986) and, therefore, are perhaps more likely to provide protection during bed rest. Greenleaf et al. used a near maximal (up to 90% of pre-bed rest  $\text{VO}_2\text{peak}$ ) interval exercise protocol (two 30-minute bouts), 5 days per week during 30 days of bed rest to prevent the loss of both  $\text{VO}_2\text{peak}$  (Greenleaf, Vernikos et al. 1992) and plasma volume (-1%, NS). Control subjects in this study experienced an average decrease in  $\text{VO}_2\text{peak}$  of 18%. The success of this protocol in bed rest prompted NASA Astronaut Strength, Conditioning, and Rehabilitation Specialists to include this protocol in their exercise prescriptions for astronauts onboard the ISS (Dr. Alan Moore, personal communication). Similar exercise countermeasure protocols have been used successfully in bed rest studies by other investigators (Lee, Bennett et al. 1997, Watenpaugh, Ballard et al. 2000, Katayama, Sato et al. 2004a, Lee, Schneider et al. 2009).

In an attempt to develop a more time-efficient exercise countermeasure protocol, Convertino et al. had subjects perform a maximal bout of supine cycle ergometry as a simulation

of exercise in microgravity at the end of a 10-day bed rest. Although  $\text{VO}_2\text{peak}$  measured during this supine ergometry test was significantly reduced from pre-bed rest values (-5.6%), when subjects performed an upright treadmill test 3 h later, they exhibited no change in treadmill  $\text{VO}_2\text{peak}$  compared with the pre-bed rest measurement (Convertino 1987). Later, it was shown that a single bout of intense exercise 24 h before resumption of normal ambulatory activities normalizes plasma volume (control: -16%, exercise: -4%, NS) (Convertino, Engelke et al. 1996) and protects LBNP tolerance (Engelke, Doerr et al. 1996) but does not prevent a decrease in  $\text{VO}_2\text{peak}$  (Engelke and Convertino 1998). It has been postulated that factors other than the exercise countermeasure, including readaptation to the upright posture, likely influenced the preservation of treadmill (Greenleaf, Bernauer et al. 1989)  $\text{VO}_2\text{peak}$  in the Convertino et al. study. Decreased muscle strength and endurance associated with bed rest deconditioning also likely affect maximal exercise performance, particularly during cycle ergometry testing when knee extensor muscles are greatly involved. For example, decreased local muscle fatigability in the calf muscles following 16 days of bed rest was correlated with a decrease in  $\text{VO}_2\text{peak}$  among control subjects (Engelke and Convertino 1998). However, few studies have directly assessed the use of a resistive exercise countermeasure to protect  $\text{VO}_2\text{peak}$ . Stremel et al. reported that subjects who performed two 30-minute sessions of static leg extension exercise (21% MVC for one minute followed by one minute of rest) during a 14-day bed rest study experienced a significant decrease in  $\text{VO}_2\text{peak}$  (-4.8%), but the loss appeared to be attenuated compared with that of both control subjects (-12.3%) and those subjects who had performed a moderate intensity aerobic exercise countermeasure (-9.2%) (Stremel, Convertino et al. 1976). Similarly, when subjects in a 30-day bed rest study performed two 30-minute bouts of maximal isokinetic exercise (10 seconds of work, 50 seconds of rest, 15 minutes per leg), supine  $\text{VO}_2\text{peak}$  was not preserved (-9.1%), but the loss was half that experienced by the control subjects (-18.2%) (Greenleaf, Bernauer et al. 1989). This partial preservation of  $\text{VO}_2\text{peak}$  using resistive exercise alone suggests that muscle strength and endurance are significant contributors to aerobic exercise performance after bed rest. Additionally, other studies that have used aerobic exercise countermeasures to prevent the decreased  $\text{VO}_2\text{peak}$  following bed rest demonstrated a protection of muscle performance (Akima, Katayama et al. 2005, Watenpaugh, O'Leary et al. 2007, Lee, Schneider et al. 2009).

### **b. Artificial Gravity**

The concept that gravitational or gravitational-like stress alone will provide some protection against the decrease in  $\text{VO}_2\text{peak}$  associated with bed rest is not new. In the 1960s, several reports were published that suggested that the amount of deconditioning associated with chair rest was less than that observed following strict bed rest (Birkhead, Blizzard et al. 1964, Lamb, Johnson et al. 1964, Lamb, Stevens et al. 1965). Later work demonstrated that exposure to a real or simulated orthostatic stress alone may attenuate the loss of upright  $\text{VO}_2\text{peak}$  during short-duration, but perhaps not longer duration, bed rest studies. Four hours of quiet standing or 3 hours of peripheral fluids shifts induced by a reverse pressure gradient garment were partially effective in protecting exercise capacity during 4 and 15 days of bed rest, respectively (Convertino, Hung et al. 1982, Vernikos, Ludwig et al. 1996). In contrast, subjects who were exposed to two 30-minute sessions of centrifugation (+2Gz) daily during 4 days of bed rest or daily multiple bouts of LBNP (-35 mmHg) during one month of bed rest experienced a similar loss of upright  $\text{VO}_2\text{peak}$  as the control subjects (Riviere, Pere et al. 1990, Iwasaki, Sasaki et al.

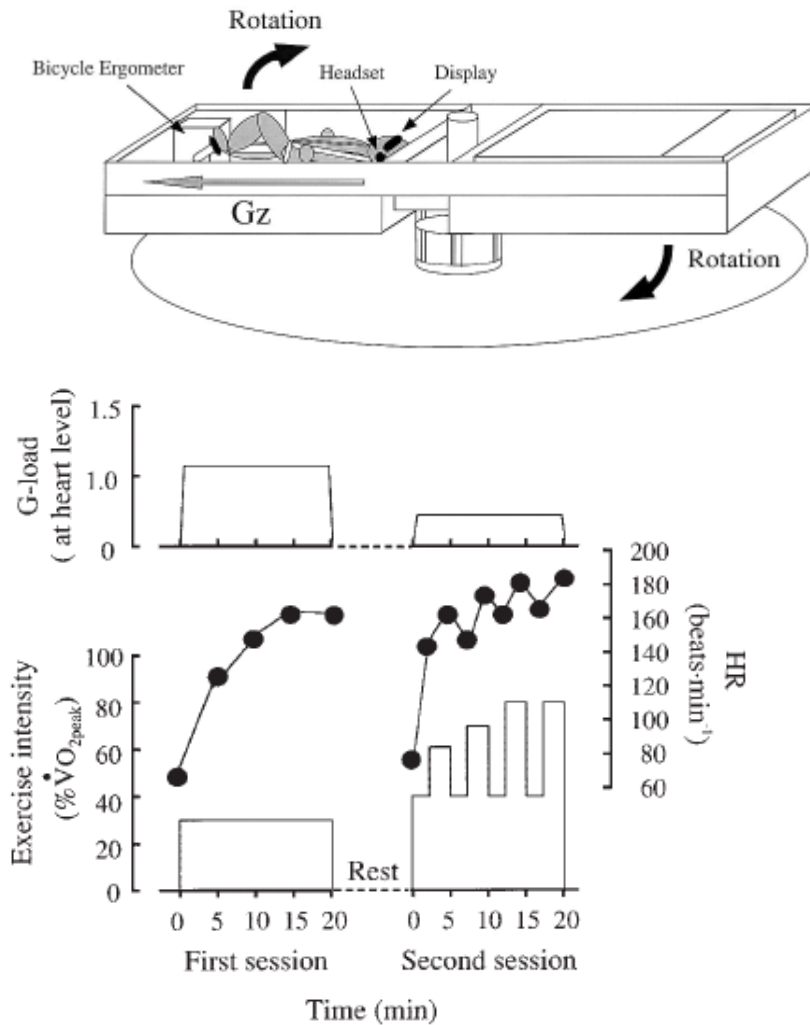
2001). These findings suggest that long-duration or more frequent exposures to orthostatic stress alone are necessary to protect against decreased post-bed rest exercise capacity.

Recently, NASA completed a 21-day bed rest study in which 15 male subjects were assigned to serve as controls or to receive an artificial gravity countermeasure generated by a short-radius human-rated centrifuge (Dr. Alan Moore, unpublished results). Countermeasure subjects were exposed to 1 h of artificial gravity per day, with a load equivalent to +2.5 G<sub>z</sub> at the feet. The subjects performed upright cycle ergometer tests to measure VO<sub>2peak</sub> before bed rest and on the first day of recovery. VO<sub>2peak</sub> was reduced by 10% in the control group but was not significantly changed in the subjects who received the artificial gravity countermeasure (-6%, NS; Dr. Alan Moore, personal communication). Following bed rest, plasma volume was reduced (-9%) in both control and countermeasure subjects, and there were no differences between the groups (Stenger, Evans et al. 2012). However, the knee and ankle extensor muscle strength of the countermeasure subjects was superior to that of the control subjects, perhaps because the countermeasure subjects performed short range of motion knee bends and heel raises during the centrifugation to protect against presyncope (Dr. Vince Caiozzo, personal communication), which may have aided in the performance of the cycle test after bed rest.

### **c. Combination Protocols**

Protection against the loss of VO<sub>2peak</sub> after bed rest is probably most effective when the simulated or real upright posture is coupled with exercise. The combination of orthostatic stress and even mild exercise reduces the countermeasure time requirement in bed rest by half to produce a similar benefit (Vernikos, Ludwig et al. 1996). The addition of a gravity-like stress during exercise training may be necessary to maintain upright exercise responses after spaceflight and bed rest (Convertino, Goldwater et al. 1982). Supine exercise may maintain plasma volume, but a gravitational component, real or simulated, may be required to maintain venous return and SV during post-bed rest exercise (Greenleaf, Vernikos et al. 1992).

Centrifugation to simulate an orthostatic stress during cycle exercise has been successfully employed to maintain upright VO<sub>2peak</sub> (Figure 20) (Katayama, Sato et al. 2004a). Subjects who performed two 20-minute sessions of combined exercise and centrifugation on alternating days of 20 days of bed rest maintained upright VO<sub>2peak</sub> values (-9±7%, NS), while those who did not perform the countermeasure experienced a significant loss (-27±7%). Countermeasure subjects exercised first for 20 minutes with a 0.8-1.4 G<sub>z</sub> load at the heart while pedaling the cycle ergometer with a constant exercise intensity of 60 Watts. A 10-minute rest period without exercise or centrifugation was then permitted before subjects began the second exercise session. Subjects experienced 0.3 g at heart level during this session and performed an interval exercise protocol similar to one that had been previously used to preserve upright exercise capacity during 14 days of bed rest (Watenpugh, Ballard et al. 2000). In addition to protecting VO<sub>2peak</sub>, cardiopulmonary responses to submaximal exercise, including HR and SV, were maintained in subjects performing exercise during centrifugation.

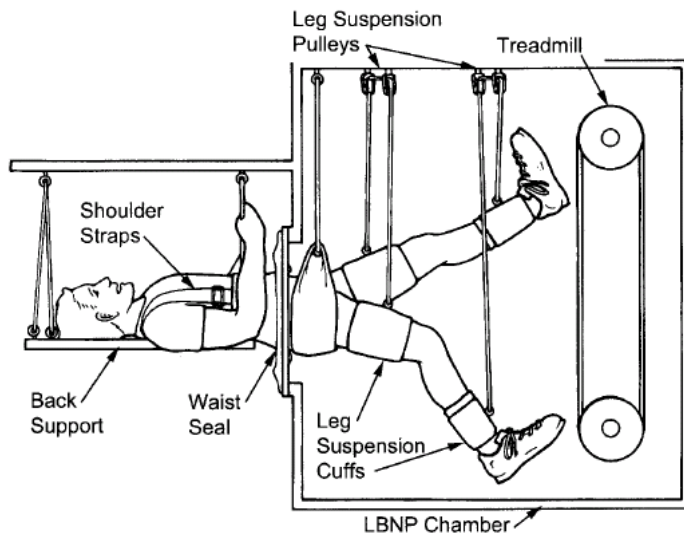


**Figure 20.** Centrifuge with cycle ergometer and the countermeasure protocol utilized by Katayama et al. to preserve upright  $\dot{V}O_{2peak}$  (Katayama, Sato et al. 2004a).

Technical and logistical barriers to continuous whole spacecraft rotation or intermittent short-radius centrifugation make near-term utilization of this centrifugation difficult; therefore, using LBNP to simulate orthostatic stress during exercise may be an attractive alternative. The use of LBNP and exercise in separate sessions during bed rest was examined during a 28-day bed rest. The countermeasure subjects participated in a protocol of light supine cycle and isokinetic exercise and LBNP (-40 mmHg for 15 minutes per day) in the latter half of a 28-day bed rest study. Countermeasure subjects appeared to receive some protection against loss of  $\dot{V}O_{2peak}$  (-6% vs. Control: -16%,  $p=0.06$ ) (Hughson, Maillet et al. 1994). Additionally, plasma volume was maintained in the countermeasure subjects but significantly reduced in the control group (Maillet, Fagette et al. 1996).

The exercise during LBNP (Figure 21) was led by a team of investigators led by Dr. Alan Hargens and Dr. Suzanne Schneider (Hargens, Whalen et al. 1991, Hargens and Watenpaugh 1996, Hargens, Groppo et al. 2002). The concept was developed in response to reports that long-duration crewmembers aboard the Mir space station exercised on the treadmill using loads equivalent to 60-70% of preflight body mass (Whalen 1993), which likely contributed to the

inability of exercise countermeasures to fully prevent reduced  $\text{VO}_2\text{peak}$  (Moore, Lee et al. 2003), bone loss (Smith, Wastney et al. 1999), postflight orthostatic intolerance (Meck, Reyes et al. 2001), and decreased muscle mass, strength, and endurance (Lee, Williams et al. 2000). Over the past decade, the investigator team has documented the safety and effectiveness of a combined LBNP and treadmill exercise countermeasure. This integrated countermeasure method combines high loads on the musculoskeletal system with upright, Earth-like distributions of transmural pressure across blood vessels (Hargens and Watenpaugh 1996). Subjects participating in these studies have comfortably run on the treadmill for up to 40 minutes daily at up to 1.2 body weights ( $\sim 60$  mm Hg) and experience dynamic loading with inertial forces on the musculoskeletal and cardiovascular systems similar to those present during upright exercise on Earth (Murthy, Watenpaugh et al. 1994, Murthy, Watenpaugh et al. 1994). In fact, metabolic and biomechanical responses of treadmill exercise within LBNP during simulated microgravity are comparable to metabolic and biomechanical responses of upright treadmill exercise on Earth (Boda, Watenpaugh et al. 2000). The LBNP and exercise countermeasure system has prevented reductions in  $\text{VO}_2\text{peak}$ , altered submaximal exercise responses, and decreased sprint performance during 5, 15, 30, and 60 days of bed rest (Lee, Moore et al. 1999, Watenpaugh, Ballard et al. 2000, Lee, Schneider et al. 2007, Schneider, Lee et al. 2009).

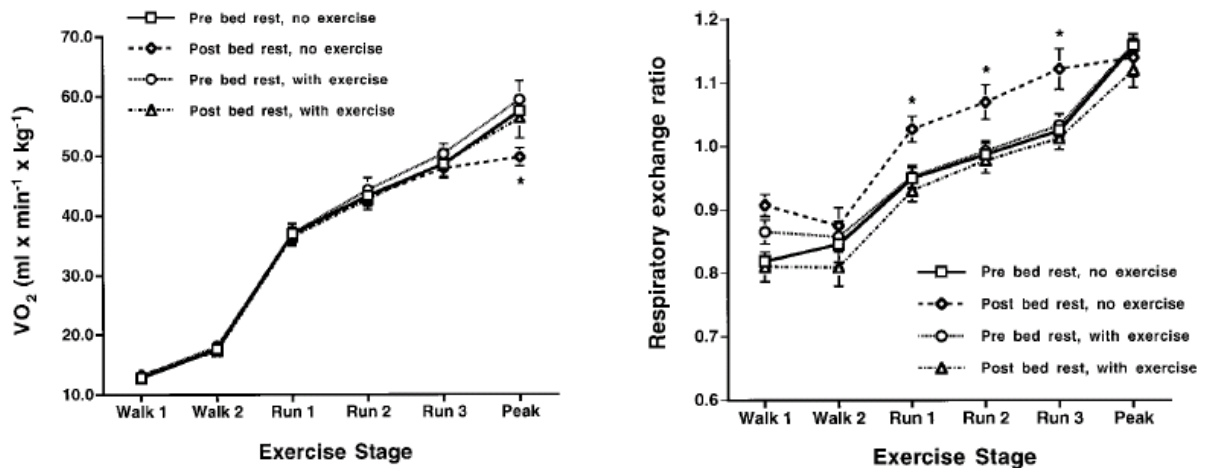


**Figure 21.** Illustration depicts the lower body negative pressure (LBNP) device. This device was used for supine treadmill exercise during bed rest for durations of 5, 15, 30, and 60 days (Lee, Moore et al. 1999, Watenpaugh, Ballard et al. 2000, Lee, Schneider et al. 2007, Schneider, Lee et al. 2009). The device consists of a vacuum control system connected to a LBNP chamber enclosing a vertically oriented treadmill. A suspension system allowed subjects to perform treadmill exercise while supine by supporting their back and legs against the downward force of gravity. A broad, flexible neoprene waist seal spans the area between the subject and the edge of the elliptical opening. The waist seal area was to equal twice the subject's waist cross-sectional area, such that the negative pressure necessary to produce one body weight equaled  $-50$  to  $-60$  mmHg.

The LBNP and exercise device was first tested in a five-day bed rest study (Lee, Bennett et al. 1997). Countermeasure subjects performed an interval exercise protocol that was modeled after one that successfully prevented a decrease in supine  $\text{VO}_2\text{peak}$  (Greenleaf, Bernauer et al. 1989) and protected plasma volume (Greenleaf, Vernikos et al. 1992) during 30 days of bed rest.

The LBNP and exercise subjects exercised daily for 30 minutes against LBNP, which provided one body weight of loading (mean: -51 mmHg). After the exercise, both the upright and LBNP exercise subjects stood (LBNP and exercise subjects experienced LBNP without exercise) for 5 minutes. The length of the bed rest was insufficient to observe a consistent change in upright  $\text{VO}_{2\text{peak}}$  in the control group, but the submaximal exercise HR, respiratory exchange ratio, and ventilation were elevated. These changes during submaximal exercise were not evident in the LBNP and exercise group. LBNP and exercise training also prevented a decrease in plasma volume, which was observed in the control group, and protected against a decrease in tolerance to 30 minutes of head-up tilt (Watenpaugh, Fortney et al. 1994).

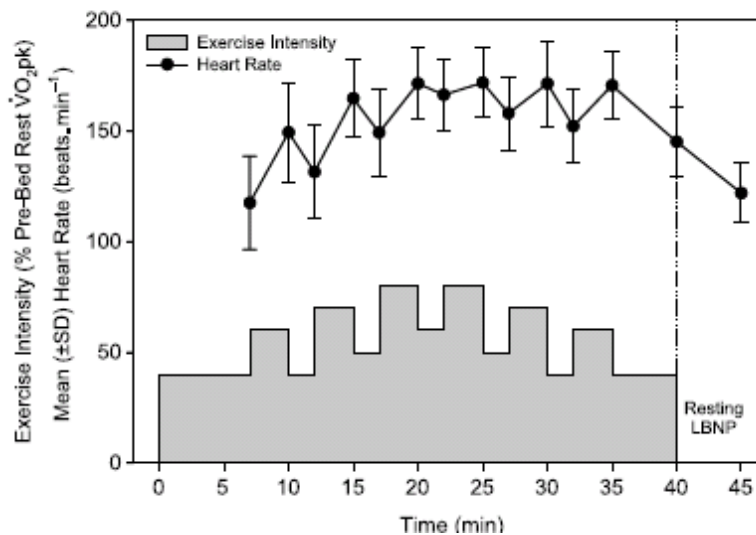
The LBNP and exercise countermeasure was tested again during 15 days of bed rest in seven subjects using a cross-over design (Watenpaugh, Ballard et al. 2000). The exercise protocol was modified by increasing the duration of the high work stages (3 vs. 2 minutes) and the total exercise time (40 vs. 30 minutes), but the target intensities were somewhat less than those in the 5-day study (peak intensity 80% vs. 90% pre-bed rest  $\text{VO}_{2\text{peak}}$ ). The post-exercise LBNP exposure was not utilized in this project, but the amount of loading provided by LBNP was increased during the study to subject tolerance (1.0-1.2 body weight). In the no exercise (control) condition, subjects experienced a significant decrease in  $\text{VO}_{2\text{peak}}$  (-14%) but had no significant change in  $\text{VO}_{2\text{peak}}$  after bed rest when they performed the LBNP and exercise countermeasure 6 days per week (-5%; Figure 22). Muscle performance also appeared to have been protected by this countermeasure; the time required to sprint 27.4 meters and plantar flexor muscle strength were maintained in the countermeasure subjects, while sprint time increased and plantar flexor strength decreased in the control subjects. Additionally, the countermeasure attenuated the post-bed rest decrease in orthostatic tolerance, as measured using a progressive LBNP protocol, compared with the losses experienced by the control subjects (Schneider, Watenpaugh et al. 2002).



**Figure 22.** Submaximal and maximal oxygen consumption ( $\text{VO}_2$ ) and respiratory exchange ratio before and after 15 days of bed rest with and without an LBNP and exercise countermeasure (Boda, Watenpaugh et al. 2000).

The LBNP and exercise countermeasure was later tested in male and female twins, one serving as the control and the sibling serving as the countermeasure subject, during 30 days of bed rest (Lee, Schneider et al. 2005, Lee, Schneider et al. 2007). The countermeasure protocol was the same as previously described in the 15-day bed rest study (Watenpaugh, Ballard et al.

2000), and the post-exercise LBNP exposure utilized in the 5-day study was also implemented (Lee, Bennett et al. 1997) (Figure 23). The investigative team hypothesized that the post-exercise orthostatic stress when the skin and muscle bed were near maximally dilated was helpful in preserving orthostatic tolerance (Schneider, Watenpaugh et al. 2002, Watenpaugh, O'Leary et al. 2007).  $\text{VO}_{2\text{peak}}$  was decreased in the control subjects after bed rest (-18%), but not in the LBNP and exercise subjects. The time required to sprint 30.5 meters and knee, ankle, and trunk extensor muscle strength were also maintained in the countermeasure subjects but not in the controls (Cao, Kimura et al. 2005, Schneider, Amorim et al. 2006). Performance of the LBNP and exercise countermeasure protocol also attenuated the decrease in orthostatic tolerance. During head-up tilt at sub-tolerance levels of orthostatic stress, SV and HR were maintained after 30 days of bed rest in the countermeasure subjects (Watenpaugh, O'Leary et al. 2007).



**Figure 23.** Mean HR response to the exercise countermeasure sessions performed by the male countermeasure (exercise plus LBNP) subjects during 30 days of bed rest (Lee, Schneider et al. 2007).

The LBNP and exercise countermeasure was tested during a 60-day bed rest period (WISE-2005: Women's International Space Simulation for Exploration), during which countermeasure subjects also performed a resistive exercise protocol. Countermeasure subjects performed the LBNP and exercise protocol an average of 3 days per week and performed supine leg press and calf press on alternate days. The same exercise protocol as in the 15- (Watenpaugh, Ballard et al. 2000) and 30-day bed rest studies (Lee, Schneider et al. 2007) was utilized during LBNP and exercise sessions, but the duration of the post-exercise LBNP stress was increased to 10 minutes. The resistive exercise protocol was designed based on a countermeasure protocol that was successful in preserving muscle strength and volume in male subjects during 29 and 90 days of bed rest (Alkner and Tesch 2004, Alkner and Tesch 2004). During a treadmill-walking test on the first day of recovery, submaximal exercise responses were preserved in the countermeasure subjects but were elevated in the controls. When a maximal treadmill exercise test was conducted on the third day of recovery,  $\text{VO}_{2\text{peak}}$  in the countermeasure subjects was not different than pre-bed rest (-3%, NS), although  $\text{VO}_{2\text{peak}}$  was significantly decreased in the control subjects (-21%). Unlike previous work, sprint performance was not tested in this study,

but ventilatory threshold was determined to be preserved in the countermeasure subjects and decreased in the controls. Knee extensor muscle strength and endurance (Lee, Schneider et al. 2014) and ankle extensor strength (Trappe, Burd et al. 2007) were also preserved with this countermeasure. Additionally, LBNPex plus resistive exercise prevented cardiac atrophy in women during a 60-day bed rest study. Left ventricular volume and long axis length were maintained in the countermeasure subjects during bed rest, and left ventricular mass, right ventricular mass, and mean wall thickness increased in these subjects (Dorfman, Levine et al. 2007).

Unfortunately, presumably due to the large budgetary requirements of performing bed rest studies with multiple groups, none of the investigations that have used a countermeasure combining orthostatic stress and exercise have utilized either a group who was exposed to orthostatic stress alone or exercise alone. Consequently, it is impossible to determine the proportional contributions of the countermeasure components, exercise alone, orthostatic stress alone, or their combination, on post-bed rest exercise performance.

## **6. Bed Rest Data Summary**

The decrease in  $\text{VO}_2\text{peak}$  during bed rest is rapid, occurring in a similar manner as the loss of plasma volume during the first two weeks of bed rest. Thereafter, decreased  $\text{VO}_2\text{peak}$  in response to bed rest progresses with a less steep rate of decay and appears influenced by central and peripheral adaptation. Ferretti et al. suggested that following long-duration bed rest, 73% of the reduction in  $\text{VO}_2\text{peak}$  can be explained by decreased oxygen transport from the lungs to the muscles, with the remaining influences equally divided between the oxygen diffusion and utilization at the cellular level (Ferretti, Antonutto et al. 1997). Bed rest investigations have demonstrated that frequent (at least 3 days per week), short bouts of intense exercise (interval-style and near maximal) during the bed rest period provide a time-efficient level of protection against this form of cardiopulmonary deconditioning and may also safeguard against negative adaptations in other organ systems. Although exercise without orthostatic stress may be beneficial, complete protection against changes in upright exercise performance may be best realized when exercise is undertaken in combination with an orthostatic stressor as provided by centrifugation or LBNP.

## **V. COMPUTER-BASED MODELING AND SIMULATION**

Because  $\text{VO}_2\text{peak}$  is primarily determined by  $Q_c$ , we would expect any factors related to heart function or plasma volume would be of functional significance. The impact of the microgravity-induced changes in both plasma volume and diastolic function are integrated into the operation of the Digital Astronaut as noted in Figure 24. The upper left curve in the panel describes the diastolic compliance of the left ventricle, as it relates transmural pressures (TMPs) to ventricular volumes. The lighter curve, as indicated by the arrow, depicts the shift in the compliance curve upon adaptation to the microgravity environment. This shift is due to the stiffness changes that occur with the fluid shifts in microgravity and a relative dehydration of the ventricular interstitial spaces. The stiffness of the left ventricle as a function of the interstitial fluid volume was described by Pogatsa and is shown in the curve in the lower part of the panel (Pogatsa 1980).



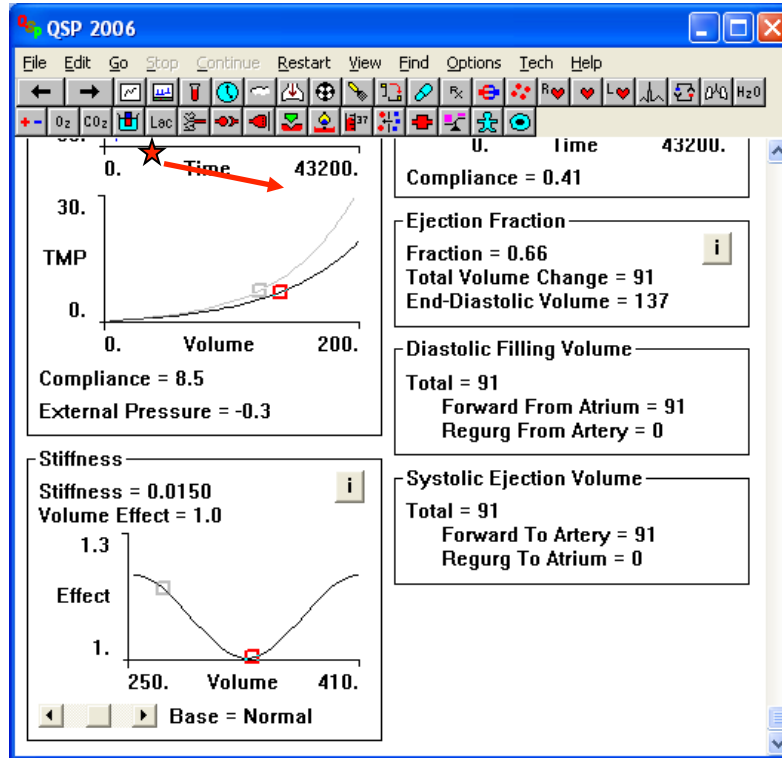


Figure 24. Simulation of microgravity effects on plasma volume and diastolic function.

Simulation studies using the Digital Astronaut Model replicate the findings demonstrated by Levine et al. of a 10% decrement in  $\text{VO}_{2\text{peak}}$  upon reentry (Levine, Lane et al. 1996). This performance validation of the model predictions allows us to extrapolate to results that may be expected for  $\text{VO}_{2\text{peak}}$  changes immediately upon entering a Mars or lunar gravitational field (Figures 25 and 26).

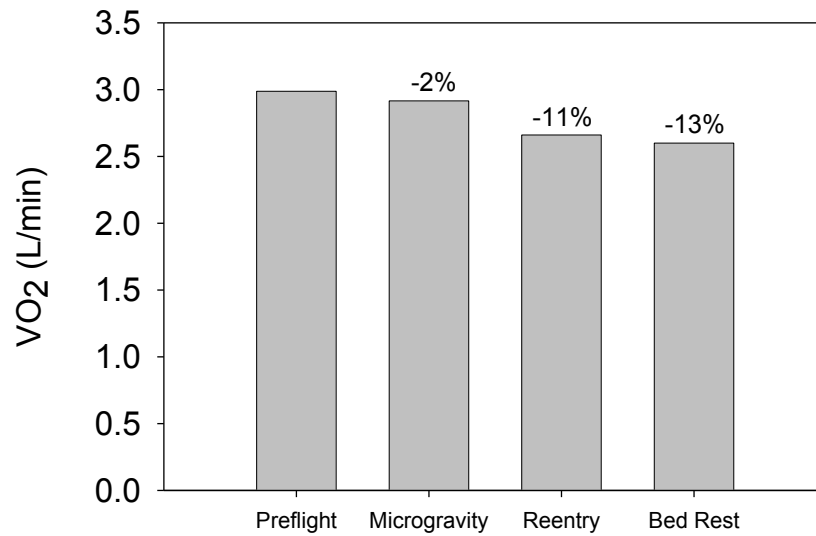


Figure 25. Simulation of the effects of spaceflight on  $VO_{2peak}$ .

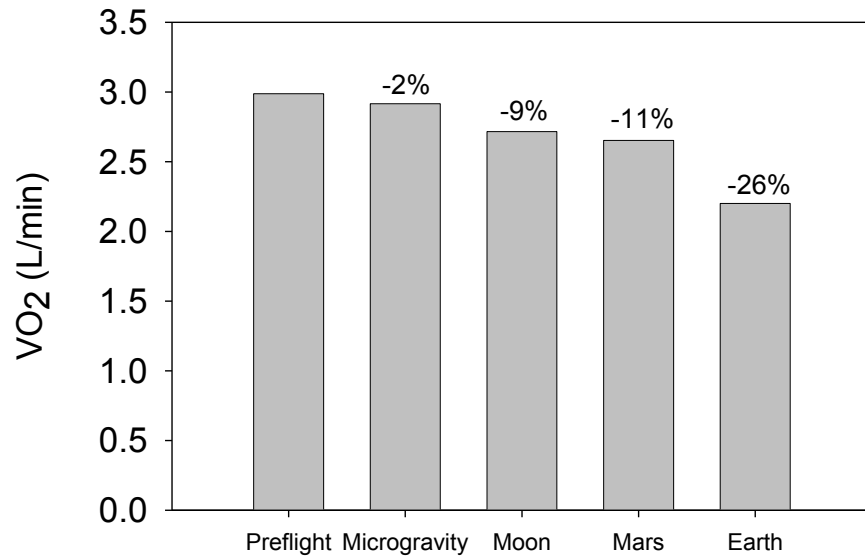


Figure 26. Model prediction of the effects of various gravity profiles on  $VO_{2peak}$ .

## VI. RISK IN CONTEXT OF EXPLORATION MISSION OPERATIONAL SCENARIOS

The principal risk of reduced  $VO_{2peak}$  is the inability of crewmembers to perform necessary extravehicular tasks, either in spaceflight or on the lunar or Martian surface. During lunar EVAs conducted during the Apollo era, EVA intensities were up to ~85% of maximum HR

during some tasks (Portree and Trevino 1997). These crewmembers were cautioned to slow their activities. However, in the future, oxygen uptake associated with building structures or accomplishing more strenuous tasks during longer stays on the moon will likely be as great as or greater than that encountered during Apollo. Furthermore, there is a risk associated with emergency egress upon return to Earth or in a partial-gravity environment (14), where maximum aerobic efforts may be required under high-stress conditions (Bishop, Lee et al. 1999).

## **VII. GAPS**

It is necessary to document the changes in  $\text{VO}_2\text{peak}$  during and following long-duration spaceflight and lunar habitation missions. The data reported by Moore et al. (Moore, Downs et al. 2014) provide novel information on the true decrements and magnitude of change in  $\text{VO}_2\text{peak}$  that occur during and after spaceflight. There is the need to address several research questions to protect the astronauts. The formal Human Research Program gaps include:

A4: Establish aerobic fitness standards for successful completion of mission tasks.

A7: Develop the most efficient exercise program for the maintenance of aerobic fitness.

A6: Develop pre-flight and in-flight evaluations to determine if aerobic standards are met.

CV2: What is  $\text{VO}_2\text{max}$  in-flight and immediately post-flight?

A9: Identify and validate exploration hardware for maintenance of aerobic fitness.

SM28: Develop a sensorimotor countermeasure system integrated with current exercise modalities to mitigate performance decrements during and after spaceflight.

EVA 6: What crew physiological & performance capabilities are required for EVA operations in exploration environments?

Closing the HRP gaps will require additional understanding with respect to specifically which measures of aerobic fitness are the most suitable for prediction of mission task performance. Accordingly, of the most predictive variables, those that are most reliably measured in-flight must be identified.

## **VIII. CONCLUSIONS**

$\text{VO}_2\text{peak}$  decreases following short- and long-duration spaceflight and after bed rest. Reduced SV, perhaps secondary to lower plasma volume and decreased diastolic filling, is believed to have a major influence on exercise capacity, especially during orthostatic stress. Although no controlled studies of exercise countermeasure effectiveness have been conducted during spaceflight, data from bed rest studies have demonstrated that countermeasures may attenuate or completely protect  $\text{VO}_2\text{peak}$  if performed at an appropriate intensity and duration.

The recently reported changes in  $\text{VO}_2$ peak during long-duration spaceflight provide critical information toward identifying fitness standards and acceptable losses in  $\text{VO}_2$ peak during flight. Although there are no reports of impaired performance of activities in microgravity, decreased aerobic fitness affects the efficiency of work and the intensity and duration for which the work can be performed. The intensity and time of future exploration tasks will likely be higher than those of current ISS EVA tasks. Crewmembers should maintain a level of fitness that provides reserve to react to emergency scenarios. Unfortunately, the required minimum level of fitness cannot be fully defined until mission scenarios, critical mission tasks, and suit design are defined.

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## **XI. LIST OF ACRONYMS**

A-V	Arterial-venous
CEVIS	Cycle Ergometer with Vibration Isolation System
DSO	Detailed Supplemental Objectives
EVA	Extravehicular activity
FD	Flight day
EDOMP	Extended Duration Orbiter Medical Project

HR	Heart rate
iRED	Interim Resistive Exercise Device
aRED	Advanced Resistance Exercise Device
ISS	International Space Station
LBNP	Lower Body Negative Pressure
NASA	National Aeronautics and Space Administration
O <sub>2</sub>	Oxygen
Q <sub>c</sub>	Cardiac output
PRD	Program Requirements Document
SLS	Spacelab Life Sciences
SV	Stroke volume
TMP	Transmural pressure
TVIS	Treadmill with Vibration Isolation System
VO <sub>2peak</sub>	Maximal oxygen uptake; maximum aerobic capacity

